Managed Care Dossier for *VESIcare*

EXECUTIVE SUMMARY

BACKGROUND

- Overactive bladder (OAB) is a highly prevalent and costly condition that significantly affects a patients' quality of life. Patient fear of leakage (driven by embarrassment and social stigma) can result in significant lifestyle modifications.
- Based on published survey results of The National Overactive Bladder Evaluation (NOBLE) study, the overall prevalence of OAB is 16.9% in women and 16.2% in men, with an increase in OAB symptoms with advancing age.
- Patients who have OAB generally complain of urinary urgency with or without incontinence, urinary frequency (≥ 8 voiding episodes per 24 hours) and nocturia (awakening ≥ 1 time per night to void).
- Antimuscarinic agents are the mainstay of OAB treatment.
- VESIcare® (solifenacin succinate) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.
- The recommended dose of *VESIcare* is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.

EFFICACY

- *VESIcare* was evaluated in four 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with a predominance of urge).
- Results of the individual studies showed that across all trials both doses of *VESIcare* statistically significantly reduced episodes of urgency, incontinence, and frequency per 24 hours, and statistically significantly increased volume voided per micturition compared with placebo.
- More than half of the patients experiencing incontinence at baseline reported no incontinence episodes at endpoint (51% of patients receiving *VESIcare* 5 mg and 52% of patients receiving *VESIcare* 10 mg compared to 34% for placebo; $P < 0.001$ for both doses).
- A long-term, 40-week open-label extension study was conducted to evaluate the safety and tolerability along with the efficacy of *VESIcare*. A total of 81% of enrolled patients completed the additional 40-week treatment period.
- A clinical trial with Solifenacin in a flexible-dose regimen compared with Tolterodine extended release as an Active comparator, was conducted in the Randomized (STAR) trial. This was a 12-week, double blind, double-dummy, comparative study to assess the efficacy and safety of *VESIcare* 5 mg or 10 mg once daily compared with tolterodine 4 mg extended release once daily in patients with OAB.
- The primary efficacy endpoint analysis of mean change from baseline to endpoint in the number of micturitions/24 hours established noninferiority of *VESIcare* compared with tolterodine extended release.
- The secondary endpoint analysis of percentage of incontinent patients at baseline reporting no incontinence episodes at endpoint established superiority of *VESIcare* (59%) compared with tolterodine extended release 4 mg (49%), as measured by 3-day patient diaries. This difference was statistically significant ($P = 0.006$).
- Other secondary endpoint analyses, mean change from baseline to endpoint in: incontinence episodes/24 hours; urge incontinence episodes/24 hours; pads used/24 hours; urgency episodes/24 hours; volume voided per micturition; and patient Perception of Bladder Condition (PBC) also demonstrated statistically significant superiority of *VESIcare* when compared with tolterodine 4 mg extended release.

SAFETY

- In placebo-controlled clinical studies, common adverse events reported in patients treated with *VESIcare* were dry mouth, constipation, blurred vision and dyspepsia, and the incidence appeared to be dose related.

- Dry mouth was reported in 4.2%, 10.9% and 27.6% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Constipation was reported in 2.9%, 5.4%, and 13.4% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Blurred vision was reported in 1.8%, 3.8%, and 4.8% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Dyspepsia was reported in 1.0%, 1.4%, and 3.9% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively.
- Overall, in placebo-controlled clinical studies, 5.4% of patients receiving placebo, 3.6% of patients receiving *VESIcare* 5 mg and 6.9% of patients receiving *VESIcare* 10 mg discontinued therapy due to all adverse events.

CONTRAINDICATIONS AND PRECAUTIONS

- *VESIcare* is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.
- *VESIcare*should be administered with caution to patients with clinically significant bladder outflow obstruction, patients with decreased gastrointestinal motility, and patients being treated for narrow-angle glaucoma.
- *VESIcare* should be used with caution in patients with reduced renal function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min).
- *VESIcare* should be used with caution in patients with reduced hepatic function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). *VESIcare* is not recommended for patients with severe hepatic impairment (Child-Pugh C).
- Do not exceed a 5 mg daily dose of *VESIcare* when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.
- In a study of the effect of *VESIcare* on the QT interval in 76 healthy women, the QT prolonging effect appeared less with *VESIcare* 10 mg than with 30 mg (3 times the maximum recommended dose), and the effect of *VESIcare* 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe *VESIcare* for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

PHARMACOECONOMICS

- The estimated costs of OAB were more than $12 billion in the year 2000.
- OAB is associated with an increased risk and prevalence of comorbidities, the most common being urinary tract infections (UTIs), falls and fractures, depression and skin infections/irritations that add significantly to the overall cost of these patients to managed care.
- In addition to the contribution of comorbidities to the cost of illness of a condition, patient persistence with therapy also influences this burden.
- In an intent-to-treat decision analysis model evaluating average 15-month costs, initial treatment with drug therapy was more cost-effective than initial behavioral therapy.
- Patient-reported outcomes were collected as secondary endpoints in an open-label, multicenter study of patients who wished to switch from tolterodine ER to *VESIcare* for the treatment of OAB symptoms. Based on the Medical Care Use Index (MCUI) data, patients experienced a significant reduction in number of physician visits, frequency of urinary tract infections, and quantity of pads/diapers used weekly from the pre-washout period to Week 12 of *VESIcare* therapy. The use of *VESIcare* resulted in improvements in medical resource utilization over pre-washout (tolterodine ER). *VESIcare* resulted in an estimated annual cost savings of $362 to $615 per patient year.
- A three-month decision-analysis model was constructed to evaluate the cost-effectiveness of antimuscarinic therapies (oxybutynin immediate release 5 mg, oxybutynin extended release 10 mg, oxybutynin transdermal 3.9 mg, tolterodine immediate release 2 mg, tolterodine extended release 4 mg, darifenacin 15 mg, *VESIcare* 5 mg, and trospium 20 mg) for the treatment of overactive bladder (OAB). Continence rates, discontinuation rates, comorbidity rates, and comorbidity treatment costs

were obtained from published literature. The results of this study suggested that *VESIcare* 5 mg was more effective and less costly than the other antimuscarinic agents.

This information is provided in response to your request for information about VESIcare® (solifenacin succinate).

VESIcare® (solifenacin succinate) is being promoted by Astellas Pharma US, Inc. (Astellas) and GlaxoSmithKline (GSK) under a co-promotion agreement. This Dossier is provided as a professional service in response to your unsolicited request. Confidential information may be provided within this Dossier. Astellas and GSK request that the recipient of this Dossier share its contents only with the Pharmacy & Therapeutics (P&T) Committee members for the purposes of making evidence-based decisions regarding the inclusion of *VESIcare* in its formulary. Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling. This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive. In order to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to Astellas at 800-727-7003. Please consult the attached Prescribing Information.

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1. PRODUCT INFORMATION

1.1 Product Description

Generic Name, Brand Name and Therapeutic Class

Generic Name: solifenacin succinate

Brand Name: VESIcare®

Therapeutic Class: muscarinic receptor antagonist

Dosage Forms, Package Sizes, NDC, and WAC

Table 1. Dosage Forms and Cost of *VESIcare*

Dosage Strength	***Description***	***Package Size***	***NDC #***	**AWP/day***	**WAC/ day†**
5 mg	Light yellow, film-coated, round tablet; debossed with logo and 150	Bottles of 30 Bottles of 90 Unit dose pack of 100‡	51248-150-01 51248-150-03 51248-150-52	$4.39	$3.51
10 mg	Light pink, film-coated, round tablet; debossed with logo and 151	Bottles of 30 Bottles of 90 Unit dose pack of 100‡	51248-151-01 51248-151-03 51248-151-52	$4.39	$3.51
*AWP = average wholesale price as of November, 2007 †WAC = wholesale acquisition cost as of November, 2007; Wholesale acquisition cost is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs. ‡Intended for institutional use only *VESIcare* tablets should be stored at 25°C (77°F) with excursions permitted from 15°C to 30°C (59-86°F)					

Product Labeling

Refer to Enclosed Prescribing Information.

AHFS or Other Drug Classification

86:12 Genitourinary Smooth Muscle Relaxants

FDA Approved Indications

VESIcare is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.(1) *VESIcare* was approved by the FDA in November 2004.

Off-Label Uses

- We are unaware of any information on this topic.

Pharmacology

The micturition process is largely mediated by cholinergic parasympathetic nervous system signaling, therefore, antimuscarinic agents are the mainstay of overactive bladder (OAB) pharmacotherapy.(2) Acetylcholine is the major peripheral neurotransmitter responsible for bladder contraction through its interaction with muscarinic receptors on the detrusor muscle of the bladder.(3) Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle, stimulation of salivary secretion and intestinal smooth muscle contractions.(4) Experimental evidence suggests OAB is linked to changes within the structure of detrusor muscle, its electrical excitability and innervation.(5) It is generally believed that symptoms associated with OAB (i.e.,

urgency and frequency often accompanied by incontinence and nocturia) are related to inappropriate and involuntary contractions of the detrusor muscle of the bladder during the filling phase.(6)

Antimuscarinic drugs interfere with involuntary detrusor contractions by targeting muscarinic receptors on the detrusor muscle. Antimuscarinic agents appear to modulate both detrusor contractions and bladder tone during the filling phase of the bladder cycle; therefore, these agents have become a mainstay of OAB treatment. *VESIcare* is a competitive muscarinic receptor antagonist indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.(1)

Muscarinic Receptor Subtypes

Muscarinic receptors are located throughout the human body and play an important role in several cholinergically mediated functions, including contractions of urinary bladder smooth muscle, stimulation of salivary secretion and intestinal smooth muscle contractions.(7) Five subtypes of muscarinic receptors have been identified (M1 through M5).

The exact location and functional role of all these subtypes is not fully clear.

Bladder

Studies have demonstrated that all five subtypes of muscarinic receptors are located in the detrusor muscle. However, the M2 and M3 receptors are the most predominant, with three times more M2 receptors than M3 receptors. Acetylcholine interacts with M2 and M3 receptors, initiating a cascade of events that result in detrusor muscle contraction. *In vitro* studies indicate that the M3 receptors are the most clinically relevant and that M2 receptors are not directly involved in contraction.

Salivary glands

M3 receptors are present in the salivary and parotid glands, M1 receptors are present in the salivary glands, and neuronal M2 and M1 receptors are present on the nerves supplying the salivary glands. High- and low-viscosity secretions and saliva volume are controlled by M3 receptors. High viscosity lubrication is controlled by M1 receptors. Thus, while salivation is predominately mediated by M1 and M3 receptors, neuronal M2 and M1 receptors also have a contributory role in salivation.

Gastrointestinal tract

While animal data suggests that all five muscarinic receptors are located in the gut smooth muscle, the M2 and M3 receptors appear to be the most relevant for humans. Similar to the bladder, M2 receptors outnumber M3 receptors (4:1 ratio) in humans. Animal data suggests that M3 receptors are primarily responsible for cholinergic stimulation of gastrointestinal motility. Therefore, antagonism of these receptors may cause a decrease in colonic transit. However, the functional role of all five receptors in the GI tract is not clear.

Brain

All five muscarinic receptors are located in the brain. Studies show that M1 receptors (and possibly M2 receptors) in the CNS have an important functional role in higher cognitive processes such as learning and memory. However, antagonism of M1 and M2 receptors in the brain is dependent on a drug's affinity for these receptors and the ability of a drug to cross the blood brain barrier.

Eye

All five muscarinic receptors are located in the human eye. Animal and human studies suggest that M3 receptors contribute to contractility responses in the iris sphincter, ciliary muscle and trabecular meshwork. Animal studies demonstrate that M5 receptors contribute to ciliary muscle contraction, and that M2 receptors may also be involved in controlling pupillary constriction and dilatation. The functional roles of M1 and M4 receptors in the eye are not clear. Similar to the brain, antagonism of muscarinic receptors is dependent not only on a drug's affinity for these receptors, but also on the drug concentration within the structures of the eye.

Muscarinic selectivity of Solifenacin

VESIcare is a competitive muscarinic receptor antagonist.(1)

The affinity of solifenacin to muscarinic receptors has been reported in the published literature. [8] [9,10,11,12] Table 2 provides the affinity of solifenacin and other antimuscarinic receptor antagonists for human muscarinic receptor subtypes. Limited conclusions can be drawn regarding the clinical significance of this information; *in vitro* activity does not necessarily correlate with clinical response.

Table 2. The affinity* of solifenacin and other muscarinic receptors antagonists for human muscarinic receptor subtypes[12]

Molecule	M1	M2	M3	M4	M5
Solifenacin	26±2.0	170±37	12±4.4	110±45	31±6.3
Tolterodine	2.7±0.23	4.2±0.51	4.4±0.45	6.6±1.7	2.5±0.49
Oxybutynin	6.1±1.5	21±3.6	3.4±0.65	6.6±2.7	18±4.0
Darifenacin	31±2.6	100±14	2.0±0.21	52±15	8.2±1.7
Propiverine	490±110	1400±220	350±53	900±200	490±120
Trospium[11]	0.75	0.65	0.50	1.0	2.3
* All values represent binding affinity estimates (Ki in nM) at recombinant muscarinic receptors. If the Ki is low, the affinity of the receptor for the inhibitor is high. Each value represents the mean±SEM of four separate experiments performed in duplicate, except for the trospium data, which was reported from a separate experiment (Hegde, et al. 2006).					

Pharmacokinetics/Pharmacodynamics

Pharmacokinetics

Absorption

After oral administration of *VESIcare* to healthy volunteers, peak plasma levels (Cmax) of solifenacin are reached within 3 to 8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg *VESIcare* tablets, respectively.[1] The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered. Animal data indicates that the absorption of solifenacin would be expected to occur throughout the digestive tract with maximal absorption occurring in the small intestine and little if any absorption occurring in the stomach.[13]

Distribution

Solifenacin is approximately 98% (in vivo) bound to human plasma proteins, principally to α_1-acid glycoprotein.[1] Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600 L.

Metabolism

Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

Excretion

Following the administration of 10 mg of ^{14}C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and in feces 4R-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45-68 hours.

Accumulation

There is no pharmacokinetic evidence that solifenacin 5 mg to 30 mg administered daily results in accumulation beyond the steady-state concentration. With once-daily multiple dosing of oral solifenacin

5 mg to 30 mg, steady-state plasma levels were attained after approximately 10 days without further accumulation.[14] Pharmacokinetic parameters do not appear to change after multiple dosing.

Onset of Efficacy

The efficacy and safety of *VESIcare* was explored in two, 4-week, randomized, double-blind parallel group, multicenter, phase II dose-finding studies. [15,16] All efficacy variables were based on information collected via patient diaries which were completed for the three days immediately preceding the visits at baseline, week 2 and week 4.

Improvements in efficacy were seen early in treatment during the first study. [15] At the Week 2 assessment, improvements in the mean change from baseline in the number of micturitions per 24 hours and volume voided per micturition were observed in the *VESIcare* 5 mg and 10 mg groups compared to placebo. After 4 weeks of treatment , a significant improvement was seen in the mean change from baseline in the number of micturitions per 24 hours and volume voided per micturition compared to placebo ($P < 0.01$ for each dose). Investigators noted that after 2 weeks of therapy, most (if not all) of the effect after 4 weeks was already achieved. Analysis of the mean change from baseline in the number of incontinence episodes per 24 hours or urgency episodes per 24 hours showed no significant difference for any dose of *VESIcare* compared with placebo.

During the second study, statistical significance was observed in the *VESIcare* 10 mg dose group, compared to placebo, beginning at the Week 2 assessment (and maintained to study end) in the mean change from baseline in the number of micturitions per 24 hours, number of incontinence episodes per 24 hours and volume voided per micturition ($P < 0.01$).[16] Statistical significance was observed in the *VESIcare* 5 mg group, compared to placebo, beginning at the Week 1 assessment (and maintained to study end) in the mean change from baseline in the volume voided per micturition ($P < 0.01$). Analysis of the mean change from baseline in the number of urgency episodes per 24 hours showed no significant difference for any dose of *VESIcare* compared with placebo. Analysis of the mean change from baseline in number of micturition episodes per 24 hours or incontinence episodes per 24 hours showed no significant difference for *VESIcare* 5 mg compared with placebo.

The most common adverse events reported in patients treated with *VESIcare* in the pivotal clinical trials were dry mouth, constipation, blurred vision and dyspepsia, and the incidence appeared to be dose-related.[1]

Use in Special Populations

Hepatic Impairment

VESIcare should be used with caution in patients with reduced hepatic function.[1] There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment. Doses of *VESIcare* greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). *VESIcare* is not recommended for patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment

VESIcare should be used with caution in patients with renal impairment.[1] There is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with severe renal impairment. Doses of *VESIcare* greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min).

Elderly

In placebo-controlled, clinical studies, similar safety and effectiveness were observed between older ($\geq$ 65 years) and younger patients (< 65 years) treated with *VESIcare*.[1] Multiple dose studies of *VESIcare* in elderly volunteers (65 to 80 years) showed that peak plasma levels (Cmax), area under the curve (AUC) and half-life ($t_{1/2}$) values were 20 to 25% higher as compared to the younger volunteers (18 to 55 years). No dosage adjustment for elderly patients is recommended.

Gender

The pharmacokinetics of solifenacin are not significantly influenced by gender.[1] No dosage adjustment based on gender is recommended.

Contraindications

VESIcare is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.(1)

Warnings/Precautions

Precautions

Bladder Outflow Obstruction

VESIcare, like other anticholinergic drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.(1)

Gastrointestinal Obstructive Disorders and Decreased GI Motility

VESIcare, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

Controlled Narrow-Angle Glaucoma

VESIcare should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Renal Function

VESIcare should be used with caution in patients with reduced renal function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr} <30 mL/min).

Reduced Hepatic Function

VESIcare should be used with caution in patients with reduced hepatic function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). *VESIcare* is not recommended for patients with severe hepatic impairment (Child-Pugh C).

Drug-Drug Interactions

Do not exceed a 5 mg daily dose of *VESIcare* when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.

Patients with Congenital or Acquired QT Prolongation

In a study of the effect of solifenacin on the QT interval in 76 healthy women, the QT prolonging effect appeared less with solifenacin 10 mg than with 30 mg (three times the maximum recommended dose), and the effect of solifenacin 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe *VESIcare* for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

Pregnancy and Lactation

Clinical Information

Pregnancy

VESIcare is classified as Pregnancy Category C.(1) In over 3000 patients enrolled in four pivotal trials that investigated the use of *VESIcare* in the treatment of overactive bladder (OAB), pregnancy, lactation, and unreliable birth control were exclusion criteria for study entry.(17)

Reproduction studies have been performed in mice, rats and rabbits.(1) After oral administration of ^{14}C-labeled solifenacin succinate to pregnant mice, drug-related material was shown to cross the placental barrier. No embryotoxicity or teratogenicity was observed in mice treated with 30 mg/kg/day (1.2 times the exposure at the maximum recommended human dose [MRHD]). Administration of solifenacin succinate to pregnant mice at doses of 100 mg/kg and greater (3.6 times exposure at the MRHD) during the major period of organ development resulted in reduced fetal body weights. Administration of 250 mg/kg/day (7.9 times exposure at the MRHD) to pregnant mice resulted in an increased incidence of cleft plate. In utero and lactational exposures to maternal doses of solifenacin succinate of 100 mg/kg/day and greater (3.6

times exposure at the MRHD) resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and delayed physical development (eye-opening and vaginal patency).

An increase in the percentage of male offspring was also observed in litters from offspring exposed to maternal doses of 250 mg/kg/day. No embryotoxic effects were observed in rats at up to 50 mg/kg/day (< 1 times exposure at the MRHD) or in rabbits at up to 50 mg/kg/day (1.8 times exposure at the MRHD). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, *VESIcare* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of *VESIcare* on labor and delivery in humans has not been studied.(1) There were no effects observed on natural delivery in mice treated with 30 mg/kg/day (1.2 times the exposure at the MRHD). Administration of solifenacin succinate at 100 mg/kg/day (3.6 times the exposure at the MRHD) or greater increased peripartum pup mortality.

Nursing Mothers

After oral administration of ^{14}C-labeled solifenacin succinate to lactating mice, radioactivity was detected in maternal milk.(1) There were no adverse observations in mice treated with 30 mg/kg/day (1.2 times the exposure at the MRHD). Pups of female mice treated with 100 mg/kg/day (3.6 times the exposure at the MRHD) or greater revealed reduced body weights, postpartum pup mortality, or delays in the onset of reflex and physical development during the lactation period.

It is not known whether *VESIcare* is excreted in human milk. Because many drugs are excreted in human milk, *VESIcare* should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue *VESIcare* in nursing mothers.

Adverse Events

Safety Results

The safety population for the four pooled studies included a total of 3027 patients (1216 placebo, 578 *VESIcare* 5 mg, 1233 *VESIcare* 10 mg).(1) The percentages of patients with treatment-emergent adverse events exceeding placebo rate and reported by 1% or more patients for combined pivotal studies are provided in Table 3. In both groups, the most common reason for discontinuation was due to adverse events (5.4% for placebo, 3.6% for *VESIcare* 5 mg and 6.9% for *VESIcare* 10 mg). The most frequent reason for discontinuation due to an adverse event was dry mouth (1.5%).

Analysis of routine clinical laboratory parameters indicated no evidence of influence of *VESIcare* on hematology analytes, clinical chemistry analytes, or urinalysis parameters.(18) Analysis of vital signs data showed no evidence of influence of *VESIcare* on systolic blood pressure, diastolic blood pressure, or pulse rate.

Table 3. Percentages of Patients with Treatment-emergent Adverse Events Exceeding Placebo Rate and Reported by 1% or More Patients for Combined Pivotal Studies(1)

SYSTEM ORGAN CLASS	**Placebo**	***VESIcare* 5 mg**	***VESIcare* 10 mg**
MedDRA Preferred Term	**(n = 1216)**	**(n = 578)**	**(n = 1233)**
Number of Patients with Treatment-emergent AE	634	265	773
GASTROINTESTINAL DISORDERS			
Dry Mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2	1.7	3.3
Dyspepsia	1	1.4	3.9
Abdominal pain upper	1	1.9	1.2
Vomiting NOS	0.9	0.2	1.1
INFECTIONS AND INFESTATIONS			
Urinary Tract Infection NOS	2.8	2.8	4.8
Influenza	1.3	2.2	0.9

SYSTEM ORGAN CLASS	**Placebo**	***VESIcare* 5 mg**	***VESIcare* 10 mg**
MedDRA Preferred Term	**(n = 1216)**	**(n = 578)**	**(n = 1233)**
Pharyngitis NOS	1	0.3	1.1
NERVOUS SYSTEM DISORDERS			
Dizziness	1.8	1.9	1.8
EYE DISORDERS			
Vision Blurred	1.8	3.8	4.8
Dry eyes NOS	0.6	0.3	1.6
RENAL AND URINARY DISORDERS			
Urinary retention	0.6	0	1.4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema lower limb	0.7	0.3	1.1
Fatigue	1.1	1	2.1
PSYCHIATRIC DISORDERS			
Depression NOS	0.8	1.2	0.8
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	0.2	0.2	1.1
VASCULAR DISORDERS			
Hypertension NOS	0.6	1.4	0.5

The overall rate of serious adverse events in the double-blind trials was 2%.[1] Angioneurotic edema has been reported in one patient taking *VESIcare* 5 mg. Compared to twelve weeks of treatment with *VESIcare*, the incidence and severity of adverse events were similar in patients who remained on drug for up to 12 months.

Post-Marketing Surveillance

The following events have been reported in association with solifenacin use in worldwide post-marketing experience: General: hypersensitivity reactions, including angioedema, rash, pruritus, and urticaria; Central Nervous: confusion and hallucinations; Cardiovascular: QT prolongation; Torsade de Pointes. Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of solifenacin in their causation cannot be reliably determined.

Other Clinical Considerations

QT Interval

Background

According to a Food and Drug Administration (FDA) Guidance document, drugs that prolong the mean QT/QTc interval by around 5 msec or less do not appear to cause Torsade de Pointes (TdP).[19] Drugs that prolong the mean QT/QTc interval by more than around 5 msec and less than 20 msec are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by greater than 20 msec have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development.

Phase 1 Clinical Study

The effect of *VESIcare* 10 mg and 30 mg on the QT interval was evaluated at the time of peak plasma concentration of *VESIcare* in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial.[1,20] Subjects were randomized to one of two treatment groups after receiving placebo and moxifloxacin sequentially. One group (n = 51) went on to complete three additional sequential periods of dosing with *VESIcare* 10, 20, and 30 mg, while the second group (n = 25) in parallel completed a sequence of placebo and moxifloxacin. Study subjects were female volunteers aged 19 to 79 years. The 30 mg dose of *VESIcare* (3 times the highest recommended dose of 10 mg) was chosen for use in this study because this dose approximates solfenacin exposure upon co-administration of *VESIcare* 10 mg with a potent CYP 3A4 inhibitor such as ketoconazole. Due to the sequential dose escalating nature of the study, baseline ECG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days.

The median difference from baseline in heart rate associated with the 10 and 30 mg doses of *VESIcare* compared to placebo was -2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analyzed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis.

The median difference from baseline in heart rate associated with the 10 and 30 mg doses of *VESIcare* compared to placebo was -2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analyzed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis. Representative results are shown in Table 4.[1]

Table 4. QTc changes in msec (90% CI) from baseline at Tmax (relative to placebo)*[1]

Drug/Dose	Fridericia method (using mean difference)
VESIcare 10 mg	2 (-3, 6)
VESIcare 30 mg	8 (4, 13)
*Results displayed are those derived from the parallel design portion of the study and represent the comparison of Group 1 to time-matched placebo effects in Group 2.	

The QT interval prolonging effect appeared greater for the 30 mg compared to the 10 mg dose of *VESIcare*.[1] Although the effect of the highest dose of *VESIcare* (3 times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

The QT interval prolonging effect appeared greater for the 30 mg compared to the 10 mg dose of *VESIcare*.[1] Although the effect of the highest dose of *VESIcare* (3 times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Phase 3 Clinical Studies

In the four pivotal phase 3 clinical studies in which more than 1800 patients were treated with *VESIcare*, ECG measurements showed a range of mean dose-related QTc interval prolongation of 1.2 to 1.9 msec with *VESIcare* 5 mg and 2.8 to 4.9 msec with *VESIcare* 10 mg. No unexpected electrocardiographic or clinical events were observed in these studies that suggested proarrhythmic activity, such as dizziness, syncope, palpitations, convulsions, or sudden death. In these studies, the changes in the QTc interval seen with *VESIcare* were not deemed to be clinically significant.[20] These observations should be considered in clinical decisions to prescribe *VESIcare* for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.[1]

Safety

Based on worldwide post-marketing safety monitoring for *VESIcare* since FDA approval in November of 2004, the FDA received two reported cases of patients with QT prolongation.[21] Additionally, there were two reports of Torsade de Pointes (TdP). No deaths occurred in these four patients. Based on the data available to Astellas, it was determined internally that these patients had multiple risk factors for QT prolongation and TdP.

CNS Adverse Events

The incidence of treatment-emergent CNS-related adverse events with *VESIcare* in the four phase 3 trials and the 40 week open-label extension trial were similar to placebo.[18,22]

Drug/Food/Disease Interactions

Drugs Metabolized by Cytochrome P450 Isoenzymes

VESIcare is extensively metabolized in the liver.[1] At therapeutic concentrations, *VESIcare* does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

CYP 3A4 Inhibitors or Inducers

In vitro drug metabolism studies have shown that solifenacin is a substrate of the cytochrome P450 3A4 (CYP3A4).[1] Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics.

Following the administration of 10 mg of *VESIcare* in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) of solifenacin increased by 1.5- and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5 mg daily dose of *VESIcare* when it is administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.

The effects of CYP3A4 inducers on the pharmacokinetics of *VESIcare* have not been studied.

Other Medications

Potential drug-drug interactions have been evaluated between *VESIcare* and oral contraceptives, warfarin, and digoxin.[1]

In the presence of *VESIcare*, there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levogestrel).[1,23] No dosage adjustment when administering *VESIcare* concomitantly with combined oral contraceptives (ethinyl estradiol/levogestrel) is recommended.

VESIcare has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin[1]. R-warfarin is a CYP3A4 substrate while S-warfarin is a substrate for CYP2C9. When subjects taking *VESIcare* were administered a single dose of warfarin, no significant effect was seen on the Cmax or total exposure ($AUC_{0-\infty}$) for R- or S-warfarin. The prothrombin time was also unchanged in the presence of *VESIcare* [1,24] No dosage adjustment when administering *VESIcare* concomitantly with warfarin is recommended.

VESIcare has no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.[1] Preclinical studies have suggested that *VESIcare* is a weak inhibitor of P-glycoprotein (P-gp), and it is generally believed that P-gp may have an effect on CYP3A4-mediated metabolism. P-glycoprotein is a membrane efflux transport protein that is widely recognized as a major determinant of the absorption and excretion of numerous drugs, including digoxin. In a study conducted in healthy men and women, a small increase in digoxin Cmax was seen following coadministration with *VESIcare*, however this difference was not statistically significant.[1,25] No dosage adjustment when administering *VESIcare* concomitantly with digoxin is recommended.

Effect of Food

There is no significant effect of food on the pharmacokinetics of solifenacin.

Dosing and Administration

The recommended dose of *VESIcare* is 5 mg once daily.[1] If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily. *VESIcare* should be taken with liquids and swallowed whole. *VESIcare* can be administered with or without food.

Splitting and Crushing

VESIcare tablets should be taken with water or other liquids and swallowed whole.[1] *VESIcare* tablets are film-coated and are not scored, making them difficult to split, crush or chew. Alternate administration techniques (i.e., chewing, splitting, cutting, breaking or crushing tablets) have not been evaluated and cannot be recommended

Dose Adjustment in Renal Impairment

For patients with severe renal impairment (CL_{cr} <30 mL/min), a daily dose of *VESIcare* greater than 5 mg is not recommended.

Dose Adjustment in Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of *VESIcare* greater than 5 mg is not recommended. Use of *VESIcare* in patients with severe hepatic impairment (Child-Pugh C) is not recommended.

Dose Adjustment CYP3A4 Inhibitors

When administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors, a daily dose of *VESIcare* greater than 5 mg is not recommended.

Access

There are no anticipated shortages, distribution restrictions, or supply limitations for *VESIcare*.

Co-Prescribed/Concomitant Therapies

Studies have not been conducted to evaluate the concomitant use of *VESIcare* with reversible cholinesterase inhibitors.

The Prescribing Information for Aricept® (donepezil HCl, Pfizer, Inc.), Cognex® (tacrine HCl, Parke Davis), Exelon® (rivastigmine tartrate, Novartis) and Razadyne® (galantamine HBr, Janssen) state that because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic agents.[26,27,28,29]This is a potential pharmacodynamic interaction and not a pharmacokinetic interaction. *Aricept*, *Cognex*, *Exelon*, and *Razadyne* are indicated for dementia associated with Alzheimer's disease. *Exelon* is also indicated for patients with dementia associated with Parkinson's disease.

There appears to be the potential for the cholinesterase inhibitor to antagonize the effects of all antimuscarinic agents, including *VESIcare*. The clinician should consider this when prescribing *VESIcare* concomitantly with cholinesterase inhibitors.

Comparison with Comparator Products

Indications

VESIcare (solifenacin succinate), *Ditropan XL* (oxybutynin chloride), *Oxytrol* (oxybutynin chloride), *Detrol* (tolterodine tartrate), *Detrol LA* (tolterodine tartrate), *Sanctura* (trospium chloride), *Sanctura XR* (trospium chloride), and *Enablex* (darifenacin) are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. *Ditropan XL* (oxybutynin chloride) is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g. spina bifida). *Ditropan* (oxybutynin chloride) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).

Pharmacology

Acetylcholine interacts with muscarinic receptors on the detrusor muscle and is the major peripheral neurotransmitter responsible for bladder contraction. Solifenacin, oxybutynin, tolterodine, trospium and darifenacin are muscarinic receptor antagonists.

Pharmacokinetics

Table 5. - See Appendix

Contraindications

VESIcare (solifenacin succinate), *Ditropan* (oxybutynin chloride), *Ditropan XL* (oxybutynin chloride), *Oxytrol* (oxybutynin chloride), *Detrol* (tolterodine tartrate), *Detrol LA* (tolterodine tartrate), *Sanctura* (trospium chloride), *Sanctura XR* (trospium chloride), and *Enablex* (darifenacin) are all contraindicated in patients with urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma.*Sanctura* (trospium chloride), *Sanctura XR* (trospium chloride), and *Oxytrol* (oxybutynin chloride) are also contraindicated in patients at risk for these conditions. In addition, *Ditropan* (oxybutynin chloride) and *Ditropan XL* (oxybutynin chloride) are contraindicated in patients with other severe decreased gastrointestinal motility conditions and in patients at risk for the conditions mentioned previously. All products are contraindicated in patients with hypersensitivity to the drug or its ingredients.

Adverse Events

In the absence of published data from comparative clinical trials, it is not possible or appropriate to compare the incidence of adverse events between *VESIcare*, oxybutynin, trospium and darifenacin. Differences in reporting rates of adverse events can reflect differences in patient populations, trial design, methods of adverse event collection and coding, among other things. One study comparing *VESIcare* and tolterodine extended release (ER) has been conducted.[30] In this study the most commonly reported treatment-emergent adverse events were dry mouth (30.0% and 24.1%), constipation (6.4% and 2.1%), headache (1.3% and 2.5%), dyspepsia (1.7% and 0.5%) and blurred vision (0.5% and 1.5%) for *VESIcare* and tolterodine ER, respectively.

Drug Interactions

Table 6. - See Appendix

Dosage and Availability

Table 7. - See Appendix

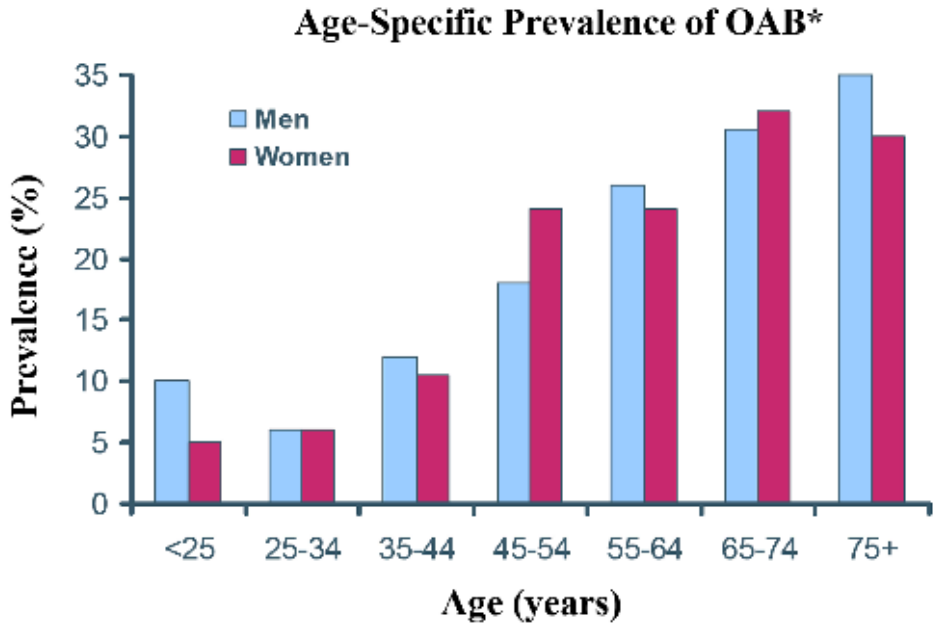
1.2 Place of Product in Therapy

Disease Description

The definition of overactive bladder (OAB) as approved by the Standardization Subcommittee of the International Continence Society (ICS) in September 2001 is defined as urgency, with or without incontinence, usually with frequency and nocturia.[6]

The results of The National Overactive Bladder Evaluation (NOBLE) have been published by Stewart et al.[31] The purpose of the NOBLE project was to develop a research definition of OAB, estimate its overall prevalence and the burden of illness, and to differentiate between OAB populations (i.e. wet vs dry patients). The telephone survey population consisted of 5204 non-institutionalized men and women ≥ 18 years of age in the United States. Dry OAB was defined as ≥ 4 episodes of urgency in the previous 4 weeks with either frequency > 8 times per day or the use of ≥ 1 coping behaviors to control bladder function. The definition of wet OAB was similar to dry OAB but included ≥ 3 episodes of non-stress related urinary incontinence in the past 4 weeks. Based on survey results, the overall prevalence of OAB was 16.9% in women and 16.2% in men, with an increase in OAB symptoms with advancing age (Figure 1). While OAB is often perceived as an "older" persons' condition, about half of those affected are 35-64 years of age. The overall prevalence of dry vs wet OAB was 7.6% vs. 9.3% in females and 13.6% vs. 2.6% in males. Based on prevalence data from the NOBLE study and population data from the US census in 2000, more than 34 million people in the United States are estimated to have OAB.[32]

Figure 1. Prevalence of OAB by Age in NOBLE Survey



***Overall prevalence, with and without urge incontinence.**
N=5204, women vs men: *P*=NS

Milson et al reported the results of a population-based prevalence study of OAB performed in France, Germany, Italy, Spain, Sweden and the United Kingdom.[33] Subjects were selected from the general population of men and women ≥ 40 years of age. Subjects were screened using a questionnaire and a 2-stage telephone procedure. Subjects with bladder control problems were first identified, and then the nature of the problem was characterized. Those subjects potentially having OAB were identified by specific questions on frequency, urgency and urge incontinence. OAB frequency was identified as > 8 micturitions in 24 hours and nocturia as getting up ≥ 2 times per night to urinate. Patients who had symptoms suggestive of prostatic obstruction, urinary tract infection or stress incontinence were excluded. Out of 16,776 subjects interviewed, symptoms suggestive of OAB were reported by 16.6% of subjects (15.6% of men and 17.4% of women). Additionally, the prevalence of OAB symptoms increased with advancing age, varying from 3.4% (40 to 44 years) to 41.9% (≥ 75 years) in men and 8.7% (40 to 44 years) to 31.3% (≥ 75 years) in women. The most commonly reported symptoms were frequency (85%), urgency (54%), and urge incontinence (36%). While 60% of respondents with symptoms had spoken with a physician, only 27% were being treated.

Cost of Illness for Overactive Bladder

Overactive bladder (OAB) is a highly prevalent and costly condition. As the population ages, the prevalence of clinical conditions such as OAB is expected to increase; indeed, an estimated 34 million Americans suffer from OAB.[34] OAB is associated with an increased risk and prevalence of comorbidities, the most common being urinary tract infections (UTI), skin infections/irritations, falls and fractures, and depression that add significantly to the overall cost of these patients to managed care.[35,36] In addition, OAB interferes with daily routines, intimacy and sexual function, causes embarrassment, and can diminish self-esteem and quality of life (QoL).[37]

Direct and Indirect Costs

Hu et al used data from the National Overactive Bladder Evaluation (NOBLE) Program to assess the economic impact of OAB in community-dwelling adults.[38] Key cost components measured were direct medical costs specific to OAB (diagnosis, routine care, treatment, etc.), costs of managing comorbid consequences of OAB (UTI, falls/fractures, skin infections, longer hospitalizations, nursing home

admissions) and indirect costs (lost productivity). This study is unique in that it is specific to OAB and costs are separated by gender and residence (community-dwelling vs. institution). From this study it was determined that the total cost of OAB across the US population, regardless of point of residence, was considerable: $12 billion in the year 2000. This study further showed that total costs for institutionalized adults with OAB were less than those for community-dwelling adults (approximately $2.8 billion vs. nearly $9.2 billion).

Total societal costs due to OAB were four times higher for women ($7.39 billion) compared with men ($1.79 billion) and costs per person were also almost four times higher for women ($410) than men ($110). Among women, older women (≥ 65 years of age) incurred greater costs than younger community-dwelling women for treatment of OAB ($1.4 billion vs. $1.1 billion) and routine care for OAB ($745 million vs. $569 million).[38] On the other hand, OAB afflicting younger community-dwelling men (< 65 years of age) was more costly than in older community-dwelling men with regard to diagnostic costs ($15.9 million vs. $8 million), routine care costs ($176 million vs. $72 million), and indirect costs ($426 million vs. $16 million).

In 1995, Wagner and Hu estimated the total cost of urinary incontinence to be $26.3 billion.[39] Of this estimate, $12.5 billion were direct medical costs (including diagnostic costs [$393.5 million], treatment costs including behavioral, drug and surgical [$728.3 million] and routine care costs [$11.4 billion]), $704 million were indirect costs, and the cost of managing comorbid conditions were the most costly component at $13.1 billion (primarily due to nursing home admissions and extended hospitalizations at $2.2 billion and $6.2 billion, respectively). In 2000, Hu et al updated the cost of general urinary incontinence provided in Wagner and Hu in 1995 US dollars to 1998 US dollars. The total cost of urinary incontinence increased to an estimated $28.4 billion.[40]

A retrospective review was conducted to determine the prevalence and cost of overactive bladder in elderly patients with Medicare coverage.[41] Data was taken from the Medicare 5% limited dataset , a random sample which included 5% of all enrolled Medicare patients. Claims were included for beneficiaries 65 or older who had Medicare Parts A and B coverage between January 1, 2003 and December 31, 2004 (N = 1,207,555). Prescription claims were excluded since Medicare did not cover retail prescriptions at the time of the study. The data was analyzed using two definitions to classify OAB patients. The base case definition included diagnosis codes which strictly defined OAB and the sensitivity variant definition included codes to help identify OAB, but may have also identified incontinence conditions.

The prevalence of OAB was 8.8% for the base definition and 13.6% for the sensitivity definition. The mean total annual expenditures in 2004 dollars for patients with OAB ranged from $9,331 to $9,655. The mean annual expenditures attributable to OAB ranged from $825 to $1,184 per patient, constituting 9% to 12% of total medical costs for OAB patients. The aggregate total expenditures attributable to OAB ranged from $1.8 to $3.9 billion per year.

Table 8. Summary of Costs Associated with OAB

Study Description	Findings
Cost of illness by Hu et al, 2003 used data from NOBLE for community-dwelling adults and one published study for institutionalized adults (includes nursing homes and long-term care facilities) [38]	Cost components(all costs presented in 2000 US dollars) • Direct costs: diagnostics + routine care (incontinent supplies, laundry, dry-cleaning) + treatment (physician visits, surgery, behavioral therapy, drug therapy) • Cost of comorbid consequences (UTI, falls, skin infections, longer hospitalizations, nursing home admissions) • Indirect costs: lost productivity Total cost in community setting: women • Direct costs: $3.9 billion ($53 million for diagnostic + $1.3 billion for routine care + $2.6 billion for treatment costs) • Cost of comorbid conditions: $3.1 billion (UTI and nursing home admissions are the biggest components at $1.2 billion and $1.5 billion, respectively) • Indirect costs: $399 million • Total costs for women: $7.39 billion • Costs higher for older women (≥ 65 years) than younger women for treatment costs ($1.4 billion vs. $1.1 billion) and routine care costs ($745 million vs. $569 million) Total cost in community setting: men • Direct costs: $533 million ($24 million for diagnostic + $248 million for routine care + $261 million for treatment costs) • Cost of comorbid conditions: $824 million (UTI and nursing home admissions are the biggest components at $186 million and $493 million, respectively) • Indirect costs: $441 million • Total costs for men: $1.79 billion • Costs higher for younger men (< 65 years) than older men for diagnostic costs ($15.9 million vs. $8 million), routine care costs ($176 million vs. $72 million), and indirect costs ($426 million vs. $16 million) Total institutional costs (men and women) • Direct costs (diagnostic + drug + routine care): 2.8 billion ($13.2 million + $3 million + $2.77 billion) • Cost of comorbid conditions (skin infections + UTI + fractures): $65 million ($9.7 million + $40.1 million + $15.2 million) Total cost of OAB • $12.0 billion ($9.2 billion in community + $2.8 billion in institutions)
Cost of illness by Hu et al, 2004 combined disease epidemiologic data with treatment rates, consequence probabilities, average cost estimates [34]	• Prevalence : 17 million (UI) vs. 34 million individuals (OAB) • Total cost: $19.5 billion (UI), $12.6 billion (OAB) (2000 US dollars) • Costs to community vs. nursing home patients for UI: $14.2 billion (community) $5.3 billion (nursing home) • Costs to community vs. nursing home patients for OAB: $9.1 billion (community) $3.5 billion (nursing home) • Total and per-person costs higher for UI because OAB patients without incontinent episodes incurred fewer costs
Cost and prevalence of OAB in elderly patients using data from Medicare claims[41]	• Prevalence: 8.8% - 13.6% of Medicare population with OAB • Mean total annual Medicare expenditures for OAB patients: $9,331 - $9,655 • Mean annual Medicare expenditures attributable to OAB: $825 - $1,184 per patient (9% - 12% of total medical costs for OAB patients) • Aggregate total Medicare expenditures attributable to OAB: $1.8 to $3.9 billion per year

Indirect Costs Related to Work Loss

Wu et al conducted a retrospective analysis to assess the indirect work loss costs of OAB from the employer's perspective.[42] Patient samples for OAB patients and matched controls were collected from an administrative claims database covering 1.2 million lives in the United States dating from 1999 through 2002. Enrollees were aged 18 and 64 years (mean age 44 years for both groups) and each had at least one ICD-9 diagnostic code to identify OAB. Sample 1, which included 3077 OAB employees, was analyzed for work loss patterns and costs. Time to disability and associated risk factors were studied in Sample 2, which included a final patient sample of 3952 OAB employees. Non-OAB controls were matched with OAB employees in each sample population at a ratio of 2:1. The analysis period was 38 weeks (9.5 months) in duration, however, analyses were extrapolated to 52 weeks (12 months).

Results showed that employees with OAB experienced higher incidences of work loss per year. A statistically significantly greater proportion of OAB patients in Sample 1 missed at least one day of work compared to non-OAB controls during the 38-week study period (90.0% vs. 75.5%, respectively, $P < 0.01$). Similarly, more OAB patients missed at least one day of work due to disability compared to the control group (7.0% vs. 4.2%, respectively, $P < 0.01$). There was a significantly greater number of work days missed for OAB employees due to medical reasons (2.2 more days) and work days missed due to disability (3.4 more days) compared to non-OAB employees ($P < 0.01$ for both). Data from a multivariate regression analysis to adjust for potential bias confirmed these results (4.4 more days for OAB patients vs. controls; $P < 0.05$). Employers paid an average of $505 more per year (a 73% increase) for each OAB employee in indirect work loss costs compared to non-OAB employees ($P < 0.05$). Data from a multivariate regression analysis to adjust for potential bias also resulted in a higher work loss burden of $391 per year for each OAB employee compared to a non-OAB employee ($P < 0.05$). The analysis of Sample 2 revealed that disability claims occurred in a shorter time period for OAB employees compared to the non-OAB control group (7% vs. 5%, respectively, within a year of diagnosis and 14% vs. 11%, respectively, within 2.5 years of a diagnosis), as evidenced by a both a log-rank test ($P < 0.01$) and a Wilcoxon test ($P < 0.01$). Overall, OAB contributed to more days away from work, shorter time to disability and greater annual indirect costs to employers.

Impact of Co-Morbidities on the Overall Cost of OAB

Darkow et al examined the cost of OAB and five commonly occurring comorbid conditions through a retrospective claims analysis of data from one managed care plan of 2.7 million members.[36] Comorbidities of interest were falls and fractures, depression, UTI, skin infections, and vulvovaginitis. Outcomes of interest for this analysis included prevalence of the comorbidities, their corresponding medical charges, and total medical costs for OAB patients.

Members of the plan who were 18 years or older (average age: 69 years), continuously enrolled in the health plan during 2001 and 2002, and had a medical claim with any ICD-9 diagnosis for OAB were considered "cases" in the analysis. "Controls" were those plan members who met the same criteria but did not have an ICD-9 diagnosis of OAB or diabetes insipidus. A random sample was then matched 1:1 to OAB patients based on propensity score. A random index date was assigned to each possible control member. A total of 11,556 OAB patients and 11,556 matched controls were identified. No significant differences between OAB patients and controls were noted with regard to patient demographics. OAB patients and controls were well matched with regard to the baseline clinical characteristics used in propensity scoring. However, the cohorts did appear to have slight differences in the proportions of members with characteristics that were not included in the matching process. Specifically, the proportion of members with neurologic conditions (such as cognitive impairment and Parkinson's disease), potentially inappropriate medication use, and prostatic hyperplasia appeared to be higher among OAB patients.

OAB patients were significantly more likely than controls to have each of the studied comorbid conditions ($P < 0.0001$). UTI was the most common comorbidity (28.0% and 8.4% of OAB patients and controls, respectively). After adjusting for UTI risk factors present during the pre-index period, OAB patients were found to be 4.3 times more likely than controls (95% CI: 3.9 – 4.6) to have a UTI. Falls and fractures were also common for both OAB patients and controls, with 25.3% of OAB patients and 16.1% of controls experiencing a fall or fracture. After adjusting for relevant confounding factors, OAB patients were observed to be 1.7 times more likely (95% CI: 1.6 – 1.8) than controls to have experienced a fall or fracture. Depression was present in 10.5% of OAB patients and in 4.9% of controls; OAB patients were

calculated to be 2.3 times more likely (95% CI: 2.1 – 2.5) than controls to have depression. Vulvovaginitis and skin infections were less common, being present in 4.7% and 3.9%, respectively, of OAB patients and 1.8% and 2.3%, respectively, of controls. OAB patients were significantly more likely than controls to have both vulvovaginitis (odds ratio [OR]: 2.7; 95% CI: 2.3 – 3.1) and skin infections (OR: 1.7; 95% CI: 1.5 – 2.0). At least one of these comorbidities was experienced by more than half of OAB patients (52.1%), while 27.9% of controls experienced one of these conditions. After adjusting for relevant confounding factors, these conditions were 2.8 times more likely (95% CI: 2.6 – 2.9; $P < 0.0001$) among OAB patients vs. control patients.

To describe the financial impact of these comorbidities, mean annual charges were also calculated for each condition among the subset of members who incurred medical charges for that condition. The comorbidity associated with the highest adjusted mean medical charges for the entire cohort was falls and fractures ($934 for OAB patients and $598 with controls). The adjusted mean medical charges related to UTI were $603 for OAB patients compared with $176 for controls. The adjusted depression-related medical charges averaged $93 in patients with OAB which was higher than mean charges related to this condition for the controls ($23). Mean medical charges related to skin infections and vulvovaginitis were low ($67 and $11, respectively, for OAB patients and $10 and $3, respectively, for controls). Mean total medical charges related to any of the comorbidities were significantly higher for OAB patients compared with controls ($P < 0.0001$). After adjustment, the mean related medical charges were $1.689 for patients with OAB and $829 for controls.

A retrospective claims analysis study was conducted to evaluate the clinical and economic impact of OAB in a population under the age of 60, in particular the prevalence and cost of related comorbidities.[43] Managed care plan members between 18 and 59 years of age, continuously enrolled in the health plan during 2002, who had a medical claim with any ICD-9 diagnosis for OAB, were followed for one year. A random sample was matched 1:1 to OAB patients based on propensity score. The primary outcome was the percentage of patients with a primary or secondary diagnosis of the following comorbidities: falls and fractures, depression, UTI, skin infections, and vulvovaginitis. In addition, mean annual submitted medical charges were calculated for the comorbidities. A total of 2750 OAB patients and 2750 matched controls were identified. Patient demographics included 73.3% of females and the mean age was 45 years of age. OAB patients were significantly more likely than controls to have a comorbid condition ($P < 0.0001$). After adjusting for risk factors, OAB patients were significantly more likely than controls to have each of the studied comorbid conditions ($P < 0.0001$ for all comparisons). The odds ratios were 4.7 for UTIs, 2.9 for vulvovaginitis, 2.5 for depression, 2.2 for skin infections and 1.6 for falls and fractures. Overall, patients with OAB were 2.8 times more likely to have at least one of the comorbid conditions ($P < 0.0001$). Mean total medical charges related to any of the comorbidities were higher for OAB patients compared with controls. The comorbidity associated with the highest adjusted mean medical charges for the entire cohort was skin infections, followed by UTIs, any comorbidity, depression, falls and fractures and vulvovaginitis.

The findings of these comorbidity studies have been validated by a second study recently completed with similar endpoints.[44] This retrospective database analysis utilized pharmacy and medical claims from a large southeastern health plan totaling approximately 750,000 lives from a health maintenance organization (HMO) and preferred provider organization (PPO) population. The intake period was defined as the period between January 1, 2001 and December 31, 2002. Members were included in the analysis if they satisfied at least one or two conditions: (1) At least one OAB diagnosis on medical claims during the intake period. The ICD 9 codes used for identification of OAB cases by claims are identical to those used in the study above; or (2) At least one prescription claim for OAB treatment drugs during the intake period. OAB treatment drugs included oxybutynin, tolterodine, and flavoxate in various dosage forms. The date of the patient's first qualifying medical claim or qualifying prescription during the intake period was identified as that patient's index date. All medical and pharmacy claims were then collected for one year pre-index date and a minimum of 1-year post-index date for qualified patients. All study patients were further required to have continuous insurance eligibility during the entire 1-year pre-index date and a minimum of a 1-year post-index date time period for study participation. This analysis utilized a matched cohort design to compare OAB cases and controls.

The full sample study cohort consisted of 12,876 (66%) females and 6,610 (34%) males. Men had a statistically significant higher mean age (58 years) compared to women (55 years). Mean follow-up time was 22.5 months from index date until study end date. The results of this analysis confirmed that

of the previous study outlined above. Although the rate of bone fractures was not different, patients with OAB were 43% more likely to experience a bone fracture versus non-OAB controls (OR = 1.43) (Note: hazard ratios reflect a relative rate of an outcome; odds ratios reflect likelihood, and have slightly different interpretations).

Patients with OAB had skin infections at rates 57% higher than patients without OAB (HR = 1.57) and were 96% more likely to have skin infection versus non-OAB controls (OR = 1.96). Patients with OAB had UTI at rates 3.5-fold as high as patients without OAB (HR = 3.55) and were almost 5-fold more likely to have UTI versus non-OAB patients (OR = 4.74). Patients with OAB had depression at rates 55% higher than patients without OAB (HR = 1.55) and were 98% more likely to have a depression event versus non-OAB controls (OR = 1.98) (Table 9).

Table 9. Relative Risk Estimation for OAB versus Non-OAB Patients[44]

Outcomes, All Events	%	Hazard Ratios (95% CI)	Odds Ratio (95% CI)
Bone Fracture			
OAB Cases	6.8	**1.15 (0.96-1.37)**	**1.43 (1.20-1.71)**
OAB Controls	4.9		
Incremental Risk	+1.9		
Skin Infections			
OAB Cases	9.2	**1.57 (1.33-1.84)**	**1.96 (1.66-2.32)**
OAB Controls	4.9		
Incremental Risk	+4.3		
Urinary Tract Infections			
OAB Cases	36.7	**3.55 (3.22-3.91)**	**4.74 (4.25-5.28)**
OAB Controls	10.9		
Incremental Risk	+25.8		
Newly-Diagnosed Depression			
OAB Cases	7.7	**1.55 (1.28-1.88)**	**1.98 (1.63-2.40)**
OAB Controls	4.1		
Incremental Risk	+3.6		

CI = confidence interval; OAB = overactive bladder; UTI = urinary tract infection

Note: n = 4,640 for each cell, except for incident depression, n = 4,035. Statistically significant results are bolded

Zorn et al examined the prevalence of depression in an OAB patient sample.[45] Approximately 30% of patients with urinary incontinence (vs. 17% of controls) suffered from depression in a prospective study ($P = 0.01$). Among patients with urge incontinence, 60% reported being depressed, a significantly higher proportion ($P < 0.001$) of patients than controls (% not reported for controls).

Treatment of OAB May Reduce Costs Associated with Co-Morbidities

A recent analysis of California Medicaid claims suggests overall health care costs (specifically those related to OAB comorbidities) can be reduced if OAB is treated [35]. According to this analysis, $3 million could be saved through the reduction of UTI post-OAB diagnosis (assuming a population incidence of UTI is 22.5% and that the cost of treating each infection is $48.50). The analysis further showed that patients who were treated for OAB required fewer services for both UTI and skin infections (2.8 and 2.0 fewer services, respectively) compared with OAB patients who discontinued therapy. These reductions translate into savings of $2.55 and $0.26 for UTI and skin infections, respectively, per member per month. A similar analysis using Illinois Medicaid claims calculated cost savings in reductions of medications and services for UTI and skin infections of approximately $200 per 2-year period during which a patient remains on pharmacotherapy for OAB.

Approaches to Treatment

Approaches to Treatment

Overactive bladder (OAB) is a highly prevalent and costly condition that significantly affects patients' quality of life (QoL). (33) (46) Driven by fear of social embarrassment, patients will primarily seek help from healthcare professionals due to incontinence. (33) These fears can significantly impact patient lifestyles. A majority of OAB patients are hindered by the upsetting prospect of becoming incontinent of urine in public. Patients often resort to coping mechanisms such as mapping out toilet facilities, limiting fluid intake, or avoiding public outings altogether.

Clinical Guidelines for general OAB syndrome (urgency, with our without urge incontinence, accompanied by frequency and/or nocturia) are unavailable. The most current published guidelines address incontinence, distinct from the other symptoms of OAB, and do not represent the expanded class of antimuscarinics available on the market today.(47,48) The initial approach in the management of the OAB patient should be to identify and treat any reversible causes of urinary incontinence. These reversible problems include urinary tract infection (UTI), atrophic vaginitis, medications such as diuretics and alpha receptor agonists, caffeine intake, psychological problems, excessive urine output and restricted mobility.(49,50) Next, the presence of complicating factors including hematuria without infection, prior radical pelvic surgery, or symptomatic pelvic prolapse should be identified and the proper course of action followed if they are identified.(50) This would include referral to a specialist and/or additional evaluation utilizing specialized procedures including urodynamic tests, endoscopic tests or imaging tests. Lastly, stress-related incontinence should be differentiated from urge incontinence and overflow incontinence (e.g. due to obstruction) ruled out.(49)

Assessment Tools for the Diagnosis of OAB

A number of tools are available to assist the physician in the diagnosis of OAB. These include asking the patient to keep a bladder diary, tracking frequency and volume voided using a pad test, assessment of post-void residual urine (PVR), urinalysis, and uroflowmetry/urodynamics (Table 10). PVR volume determination is useful when retention of urine is suspected, such as in men with benign prostatic hyperplasia (BPH), patients with neurogenic conditions affecting the lower urinary tract, or in patients having recent pelvic surgery.(3,6,49,50,51)

Table 10. Evaluation Tools for Suspected OAB(3,6,49,50,51)

Evaluation Tools	Differential Feature(s)	Comments
Bladder Diary	Frequency, urgency, nocturia, incontinence	Records episodes of frequency, urgency, incontinence, nocturia, etc.
Pad Test	> 8 g/24 hours is considered abnormal	Patient wears a pad for a predetermined period of time and changes as desired; pads are placed into individual bags and sealed. Contribution of incontinent urine to pad weight then determined per 24 hours
Post-Void Residual (PVR) Volume	>200 mL is considered abnormal	Determined by catheterization or ultrasound; especially advised for older men with hesitancy, intermittency, or weak stream symptoms; may be determined by direct catheterization or post-void ultrasound
Urinalysis	Pyuria, bacteriuria, hematuria are abnormal findings	Presence of these findings may indicate alternate pathologies such as infections or stones. It is important to rule out a urinary tract infection (UTI) since many OAB and UTI symptoms are similar

Uroflowmetry/Urodynamics*	Spontaneous or provoked involuntary contractions of the bladder indicate OAB	Objective evidence of storage and emptying functions of the bladder; very useful to rule out obstruction; useful for patients with urinary retention or neurological disorders
*Usually performed by urology specialists		

The management of OAB typically includes both non-pharmacologic and pharmacologic interventions.[3] At the initiation of therapy, patients are instructed to keep track of their symptoms with a bladder diary, allowing them to assess efficacy of treatment strategies and actively participate in their management.

Non-pharmacologic Strategies

Non-pharmacologic interventions, such as fluid management, bladder behavior training, biofeedback, and pelvic floor exercises, should be an integral part of the initial treatment of OAB (Table 11).[3,50] These simple, inexpensive, and effective strategies may be used alone or in combination with pharmacotherapy. With regard to fluid management the patient may be instructed to reduce nighttime fluids in order to manage nocturia and also to decrease or eliminate bladder irritants such as caffeine, alcohol and nicotine.

Table 11. Non-Pharmacologic Interventions in Patients with OAB[3,50]

Intervention	Important Elements	Comments
Bladder Behavior Training	Structured program of scheduled voiding with increasingly longer timed periods between voids	Requires patient to resist urge to void until scheduled time
Biofeedback	Sensations alert patient to increases in intravesical pressure; patient learns to reflexively inhibit bladder contraction(s)	Several protocols can be utilized; should be combined with other methods
Pelvic Floor Exercises	Progressive pelvic resistance exercises improve muscle tone	Originally popularized by Kegel
Absorbent Pads and Undergarments	Effective and acceptable in refractory patients	Maintains good hygiene and prevents embarrassment
Surgical Procedures	Motor-nerve ablation and augmentation cystoplasty	Only used in the patients with the most severe symptoms

Although these behavioral techniques are an important component of OAB management, many patients will require some form of pharmacotherapy. However, non-pharmacologic techniques may be continued. Combinations of behavioral and pharmacologic management strategies have been shown to improve the symptoms of OAB and reduce episodes of incontinence by > 80%. [52]

Pharmacotherapy

With regard to pharmacotherapy, antimuscarinic agents have become the mainstay of OAB treatment.[50,53] While many anticholingeric agents, such as hyoscyamine, dicyclomine and propantheline, have been used in the past to treat OAB, newer agents, such as Ditropan XL® (oxybutynin chloride), Oxytrol® (oxybutynin transdermal system), Detrol®LA (tolterodine tartrate), Sanctura® (trospium chloride), Enablex® (darifenacin) and *VESIcare*® (solifenacin succinate), are currently used to treat OAB.[54]

Other medications that have been used to treat the symptoms of OAB include imipramine (mixed urge-stress incontinence) and desmopressin, as well as estrogen for women (topical and oral) and alpha-blockers for men (useful in benign prostatic hyperplasia).[3]

Expected Outcomes of Therapy

Treatment of OAB should result in increased bladder capacity and an associated increase in the volume voided, also treatment should result in a reduction in the number of involuntary bladder contractions; and therefore, a decrease in urgency, frequency, and urge incontinence.[50] Therapy should result in restoration

of continence for patients experiencing incontinence at baseline. Additionally, it is possible that the improvement in the symptoms of OAB may result in the improvement of OAB patients' quality of life.[46] Patient-reported outcomes such as the Patient Perception of Bladder Condition (PBC) score, and Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire (OAB-q) score, Work Productivity Assessment Index (WPAI), Medical Care Use Index (MCUI), and the Health Utilities Index (HUI) have been used in clinical trials to assess treatment satisfaction, health-related quality of life, and symptom improvement.[55,56] This link between treatment of OAB and improvement in quality of life needs further study.

1.3 Pharmacogenomic Tests and Drugs

- We are unaware of any information on this topic.

2. SUPPORTING CLINICAL AND ECONOMIC INFORMATION

2.1 Key Clinical Studies

Pivotal Studies

VESIcare was evaluated in four 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with a predominance of urge).[57,58,59,60,61,62] Studies 015 and 018 compared both *VESIcare* 5 mg and 10 mg to placebo.[59,60,61,62] Study 015 also included tolterodine as an active comparator.[59,60] Studies 013 and 014 compared *VESIcare* 10 mg to placebo.[57,58] The primary aim of the studies was to assess the efficacy of *VESIcare* in patients with an overactive bladder; the secondary aim of the study was to assess the safety and the tolerability of *VESIcare*.[57,58,59,60,61,62] The studies were comprised of a single-blind, 2-week placebo run-in period, followed by a randomized, double-blind, placebo controlled, 12-week treatment period.

The study population in all 4 trials consisted of male and female patients aged ≥ 18 years with symptoms of overactive bladder (including urinary frequency, urgency or urge incontinence) for ≥ 3 months. In addition, patients had to have a micturition frequency of ≥ 8 times per 24 hours on average during the 3-day micturition diary period preceding visit 2. Patients also had to experience at least 1 of the following symptoms during the 3-day micturition diary period: an average of at least 1 incontinence episode per 24 hours or an average of at least 1 urgency episode per 24 hours.

In Studies 015 and 018, exclusion criteria were clinically significant outflow obstruction; post-void residual volume of > 200 mL; stress incontinence or mixed incontinence where stress was the predominant factor; patients with a neurological cause for detrusor overactivity; evidence of a urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; non-drug treatment including electrostimulation therapy or start of a bladder training program during the 2 weeks prior to or during the study; use of drugs intended to treat urinary incontinence; diabetic neuropathy; and contraindication to anticholinergic therapy.[59,60,61,62] In Studies 013 and 014, exclusion criteria were stress incontinence or stress-predominant mixed incontinence; post-void residual of volume of > 150 mL; active or recurrent urinary tract infection; history of bladder neoplasm or interstitial cystitis; neurogenic dysfunction of injury which could affect the lower urinary tract; treatment with electrostimulation, biofeedback, or behavioral therapy; taking any medication to treat urinary incontinence; or contraindication to anticholinergic therapy.[57,58]

The primary efficacy endpoint for all of the trials was mean change from baseline in number of micturitions per 24 hours (urinary frequency).[57,58,59,60,61,62] Secondary efficacy endpoints included mean change from baseline in number of incontinence episodes per 24 hours, mean change from baseline in volume voided per micturition and mean change from baseline in number of urgency episodes per 24 hours. The safety of *VESIcare* was evaluated on the basis of incidence and severity of adverse events, ECG parameters, laboratory parameters (including hematology, biochemistry, urinalysis and urine culture), vital signs, and post-void residual volume. All efficacy variables were based on information collected via patient diaries, which were completed for the 3 days immediately preceding the visits at baseline, week 4, week 8, and week 12. Prior to the 3-day diary collection period, the study center contacted the patient by telephone to remind him or her to begin recording the diary data. The patient recorded each micturition, each

incontinence episode, the volume voided per micturition, and each urgency episode. For micturitions, incontinence episodes, and urgency episodes, diary information was recorded daily during the 3-day period; volume voided per micturition was recorded during any 2 of the 3 days. When recording micturitions, patients also filled out a check box indicating whether or not the micturition woke the patient from sleep.

The protocols for these four pivotal studies were similar, which allowed for the pooling of results.[17,63] The four pivotal studies are described separately below, followed by a summary of the pooled analysis. Results of these studies showed that once-daily doses of *VESIcare* 5 mg and 10 mg statistically significantly reduced episodes of urgency, incontinence, and frequency per 24 hours, and statistically significantly increased volume voided per micturition compared with placebo.

Study 015 EU

Study Design

Patients were randomized to treatment with *VESIcare* 5 mg once daily, *VESIcare* 10 mg once daily, tolterodine 2 mg twice daily as an active treatment arm, or placebo in Study 015.[59,60] A tolterodine active treatment arm was included in this study, however, the study was not powered to show treatment differences between the active treatment arms. Therefore, no formal statistical comparisons between the active treatments can be made. The full analysis set (FAS) was comprised of 1033 randomized patients who received at least 1 dose of study medication and for whom primary efficacy data at the baseline visit and at least 1 on-treatment visit was available.[59,60] A total of 253 patients received placebo, 266 patients were treated with *VESIcare* 5 mg, 264 patients with *VESIcare* 10 mg, and 250 with tolterodine 2 mg twice daily. Demographic characteristics were similar for the 3 arms, with the majority of patients being women (approximately 75%) and Caucasian (98%), with a mean age of approximately 57 years. Discontinuation rates were 12% for the placebo group, 10% for the *VESIcare* 5 mg group, 7% for the *VESIcare* 10 mg group, and 10% for the tolterodine group; in all groups, the most common reason reported for discontinuation was due to adverse events.

Efficacy Results

Study results are presented in Table 12.

Table 12. Mean Change from Baseline to Endpoint for *VESIcare*, Tolterodine and Placebo: 905-CL-015 [59,60]

Parameter	*VESIcare* 5 mg (n = 266) Mean	*VESIcare* 10 mg (n = 264) Mean	Placebo (n = 253) Mean	Tolterodine 2 mg bid‡ (n = 250) Mean
Urinary Frequency (Number of Micturitions / 24hours)*				
Baseline	12.1	12.3	12.2	12.1
Reduction	2.2	2.6	1.2	1.9
P value vs. placebo	<0.001	<0.001		0.004
Number of Incontinence Episodes / 24 hours†				
Baseline	2.6	2.6	2.7	2.3
Reduction	1.4	1.5	0.8	1.1
P value vs. placebo	<0.01	<0.01		0.017
Volume Voided per micturition [mL]†				
Baseline	149.6	147.2	143.8	147
Increase	32.9	39.2	7.4	24.4
P value vs. placebo	<0.001	<0.001		<0.001
Number of Urgency Episodes / 24 hours†				
Baseline	5.8	5.8	5.3	5.5

*Primary endpoint

†Secondary endpoint

‡A tolterodine active treatment arm was included in this study, however, the study was not powered to show treatment differences between the active treatment arms. Therefore, no formal statistical comparisons between the active treatments can be made.

Reduction	2.9	3.1	1.4	2.1
P value vs. placebo	<0.001	<0.001		0.043

*Primary endpoint

†Secondary endpoint

‡A tolterodine active treatment arm was included in this study, however, the study was not powered to show treatment differences between the active treatment arms. Therefore, no formal statistical comparisons between the active treatments can be made.

Safety Results

The majority of adverse events reported were anticholinergic in nature. [59,60] Dry mouth was reported by 14% and 21.3% of patients treated with *VESIcare* 5 mg and 10 mg, respectively, and by 18.6% and 4.9% of patients in the tolterodine 2 mg twice daily and placebo treatment groups, respectively. Constipation was reported by 7.2% and 7.8% of patients treated with *VESIcare* 5 mg and 10 mg, respectively, and by 2.7% and 1.9% of patients in the tolterodine 2 mg twice daily and placebo treatment groups, respectively. Blurred vision was reported by 3.6% and 5.6% of patients treated with *VESIcare* 5 mg and 10 mg, respectively, and by 1.5% and 2.6% of patients in the tolterodine 2 mg twice daily and placebo treatment groups, respectively. Dyspepsia was reported by 1.4% and 2.2% of patients treated with *VESIcare* 5 mg and 10 mg, respectively, and by 1.1% and 0.4% of patients in the tolterodine 2 mg twice daily and the placebo treatment groups, respectively (Table 13).

There were no clinically relevant effects observed on laboratory safety parameters, vital signs or PVR.

Table 13. Treatment-Related* Adverse Events Reported by ≥ 2% of Patients in any Treatment Group (Safety Population, N = 1077) [59,60]

System Organ Class **Preferred term**	***VESIcare* 5 mg** **n = 279** **%**	***VESIcare* 10 mg** **n = 268** **%**	**Placebo** **n = 267** **%**	**Tolterodine 2 mg bid†** **n = 263** **%**
Eyes Disorders				
Vision blurred	3.6%	5.6%	2.6%	1.5%
Gastrointestinal Disorders				
Abdominal pain upper	0.7%	2.6%	1.5%	1.50%
Constipation	7.2%	7.8%	1.9%	2.7%
Dry mouth	14%	21.3%	4.9%	18.6%
Dyspepsia	1.4%	2.2%	0.4%	1.1%
Nervous System Disorders				
Headache NOS	1.1%	2.2%	1.5%	1.5%

NOS = not otherwise specified

*Events judged by the investigator possibly or probably related to study drug as well as events for which no relationship was recorded

†A tolterodine active treatment arm was included in this study, however, the study was not powered to show treatment differences between the active treatment arms. Therefore, no formal statistical comparisons between the active treatments can be made.

Study 018 EU

Study Design

Study 018 assessed the efficacy and safety of daily oral administration of*VESIcare* 5 mg and 10 mg versus placebo in male and female patients with overactive bladder. [61,62] The safety population contained 907 patients, of which 301 patients received placebo, 299 patients were treated with *VESIcare* 5 mg once daily, and 307 patients with *VESIcare* 10 mg once daily.[61,62] The FAS comprised 857 randomized patients who received at least 1 dose of study medication and for whom primary efficacy data at the baseline visit and at least one treatment visit was available. Demographic characteristics were similar for the 3 arms, with the majority of patients being women (approximately 82%) and Caucasian (97%), with a mean age of

approximately 56 years. The proportion of patients discontinuing from the study was 8.9% and was comparable across treatment groups (10.6% placebo, 8% *VESIcare* 5 mg, 8.1% *VESIcare* 10 mg).

Efficacy Results

Study results are presented in Table 14.

Table 14. Mean Change from Baseline to Endpoint for *VESIcare* 5 mg and 10 mg Daily and Placebo: 905-CL-018 (61,62)

Parameter	**Placebo (n = 281) Mean**	***VESIcare* 5 mg (n = 286) Mean**	***VESIcare* 10 mg (n = 290) Mean**
Urinary Frequency (Number of Micturitions / 24 hours)*			
Baseline	12.3	12.1	12.1
Reduction	1.7	2.4	2.9
P value vs. placebo		<0.001	<0.001
Number of Incontinence Episodes / 24 hours†			
Baseline	3.2	2.6	2.8
Reduction	1.3	1.6	1.6
P value vs. placebo		<0.01	0.016
Volume Voided per micturition [mL]†			
Baseline	147.2	148.5	145.9
Increase	11.3	31.8	36.6
P value vs. placebo		<0.001	<0.001
Number of Urgency Episodes / 24 hours†			
Baseline	5.6	6	5.5
Reduction	2.1	3	3
P value vs. placebo		0.005	0.0001
*Primary endpoint †Secondary endpoint			

Safety Results

The majority of adverse events reported were anticholinergic in nature. (61,62) The most commonly reported adverse events were dry mouth (7.7% and 23.1% of the patients treated with *VESIcare* 5 mg and 10 mg, respectively, compared with 2.3% of the placebo-treated patients), constipation (3.7% and 9.1% of the patients treated with *VESIcare* 5 mg and 10 mg, respectively, and 2% in the placebo treatment group), blurred vision (4.0% and 5.9% in the patients treated with *VESIcare* 5 mg and 10 mg, respectively, and 2.3% in the placebo group) and dyspepsia (1.3% and 2% of the patients treated with *VESIcare* 5 mg and 10 mg, respectively, compared with 0.7% of the placebo-treated patients) (Table 15).

There were no clinically relevant effects observed on laboratory safety parameters, vital signs or PVR.

Table 15. Treatment-Related* Adverse Events Reported by ≥ 2% of Patients in any Treatment Group (Safety Population, N = 907) (61,62)

System Organ Class Preferred term	**Placebo n = 301 %**	***VESIcare* 5 mg n = 299 %**	***VESIcare* 10 mg n = 307 %**
Eyes Disorders			
Vision blurred	2.3%	3.7%	5.5%
Gastrointestinal Disorders			
Constipation	2%	3.3%	8.8%
*Events judged by the investigator possibly or probably related to study drug as well as events for which no relationship was recorded			

System Organ Class **Preferred term**	**Placebo** **n = 301** **%**	***VESIcare* 5 mg** **n = 299** **%**	***VESIcare* 10 mg** **n = 307** **%**
Dry mouth	2.3%	7.4%	23.1%
Dyspepsia	0.7%	1.3%	2%
*Events judged by the investigator possibly or probably related to study drug as well as events for which no relationship was recorded			

Study 013 US

Study Design

Study 013 assessed the efficacy and safety of daily oral administration of *VESIcare* 10 mg versus placebo in male and female patients with overactive bladder.[1,57] A total of 672 patients were randomized and received at least 1 dose of study drug, placebo (n = 332) and *VESIcare* 10 mg (n = 340), and was followed as the full safety population; the FAS was made up of 615 patients, placebo (n = 309) and *VESIcare* 10 mg (n = 306).[57] Demographic characteristics were similar for the 3 arms, with the majority of patients being female (82%) and Caucasian (83%), with a mean age of 58 years. The percentage of patients who prematurely discontinued from the treatment period was similar in both groups (18% for placebo; 21% for *VESIcare* 10 mg). In both treatment groups, the most common reason for discontinuation was due to adverse events (5% for placebo; 11% for *VESIcare* 10 mg).

Efficacy Results

Study results are presented inTable 16.

Table 16. Mean Change from Baseline to Endpoint for *VESIcare* 10 mg Daily and Placebo: 905-CL-013[57]

Parameter	**Placebo** **(n= 309)** **Mean**	***VESIcare* 10 mg** **(n = 306)** **Mean**
Urinary Frequency (Number of Micturitions / 24 hours)*		
Baseline	11.5	11.7
Reduction	1.5	3
P value vs. placebo		<0.001
Number of Incontinence Episodes / 24 hours†		
Baseline	3	3.1
Reduction	1.1	2
P value vs. placebo		<0.001
Volume Voided per micturition [mL]†		
Baseline	190.3	183.4
Increase	2.7	47.2
P value vs. placebo		<0.001
Number of Urgency Episodes / 24 hours†		
Baseline	7.2	6.9
Reduction	2.5	4.1
P value vs. placebo		<0.001
*Primary endpoint †Secondary endpoint		

Safety Results

Common adverse events reported with *VESIcare* 10 mg were dry mouth (4% for placebo vs 27% for *VESIcare*), constipation (3% for placebo vs 17% for *VESIcare*), blurred vision (1.2% for placebo vs 4% for *VESIcare*) and dyspepsia (0.3% for placebo vs 3.8% for *VESIcare*) (Table 17).[57]

Minor fluctuations in vital signs and laboratory parameters appeared comparable for the two treatment groups. Overall, none of the changes appeared to be clinically meaningful or suggested that *VESIcare* had any effect on vital signs or laboratory parameters.

Table 17. Treatment-Related* Adverse Events Reported by ≥ 2% of Patients in any Treatment Group (Safety Population, N = 672)[57]

System Organ Class **Preferred term**	**Placebo** **n = 332** **%**	***VESIcare*10 mg** **n = 340** **%**
Eye disorders		
Vision blurred	1.2%	3.2%
Gastrointestinal disorders		
Dry mouth	3.6%	25.6%
Constipation	3.3%	16.2%
Nausea	1.8%	3.2%
Dyspepsia	0.3%	3.8%
Diarrhea NOS	2.4%	1.2%
Nervous System Disorder		
Headache NOS	3.9%	2.6%
Dizziness	0.9%	2.1%

NOS = not otherwise specified

* Events judged by the investigator possibly or probably related to study drug as well as events for which no relationship was recorded

Study 014 US

Study Design

Study 014 assessed the efficacy and safety of daily oral administration of *VESIcare* 10 mg versus placebo in male and female patients with overactive bladder. [58] A total of 634 patients were randomized and received at least 1 dose of study drug, placebo (n = 316) and *VESIcare* 10 mg (n = 318). The FAS was made up of 593 patients, placebo (n = 295) and *VESIcare* 10 mg (n = 298) (8). Demographic characteristics were similar for the 3 arms, with the majority of patients being female (82%) and Caucasian (90%), with a mean age of 60 years. The percentage of patients who prematurely discontinued from the treatment period was similar in both groups (14% for placebo; 15% for *VESIcare* 10 mg). In both treatment groups, the most common reason reported for discontinuation was due to adverse events (5% for placebo; 9% for *VESIcare* 10 mg).

Efficacy Results

Study results are presented in Table 18.[58]

Table 18. Mean Change from Baseline to Endpoint for *VESIcare* 10 mg daily and Placebo: 905-CL-014[58]

Parameter	**Placebo** **(n = 295)** **Mean**	***VESIcare* 10mg** **(N = 298)** **Mean**
Urinary Frequency (Number of Micturitions / 24 hours)*		
Baseline	11.8	11.5
Reduction	1.3	2.4
P value vs. placebo		<0.001
Number of Incontinence Episodes / 24 hours†		
Baseline	2.9	2.9
Reduction	1.2	2

*Primary endpoint

†Secondary endpoint

Parameter	**Placebo (n = 295) Mean**	***VESIcare* 10mg (N = 298) Mean**
P value vs. placebo		<0.001
Volume Voided per micturition [mL]†		
Baseline	175.7	174.2
Increase	13	46.4
P value vs. placebo		<0.001
Number of Urgency Episodes / 24 hours†		
Baseline	6.8	6.3
Reduction	1.8	3.3
P value vs. placebo		<0.001
*Primary endpoint †Secondary endpoint		

Safety Results

Common adverse events reported with *VESIcare* were dry mouth (6% for placebo vs 38% for *VESIcare*), constipation (4% for placebo vs 19% for *VESIcare*), blurred vision (1.3% for placebo vs 4% for *VESIcare*) and dyspepsia (0.9% for placebo vs 4.1% for *VESIcare*) (Table 19).[58]

Minor fluctuations in vital signs and laboratory parameters appeared to be comparable for the two treatment groups. Overall, the changes did not appear to be clinically meaningful and there was no indication that *VESIcare* had an effect on vital signs or laboratory parameters.

Table 19. Treatment-Related* Adverse Events Reported by ≥ 2% of Patients in any Treatment Group (Safety Population, N = 634)[58]

System Organ Class Preferred Term	**Placebo (N = 316) %**	***VESIcare* 10 mg (N = 318) %**
Gastrointestinal Disorders		
Dry mouth	5.7%	37.1%
Constipation	3.8%	17.6%
Nausea	1.3%	4.1%
Dyspepsia	0.9%	4.1%
Nervous System Disorders		
Headache NOS	2.2%	1.9%
Dizziness	2.2%	0.3%
Eye Disorders		
Vision blurred	1.3%	3.1%
Dry eye	1.3%	3.8%
Renal and Urinary Disorders		
Urinary retention	0.9%	2.8%
NOS= not otherwise specified *Events judged by the investigator possibly or probably related to study drug as well as events for which no relationship was recorded		

Pooled Analysis of Pivotal Studies

Study Design

VESIcare was evaluated in four 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical studies for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with a predominance of urge).[1]

These studies involved 3027 patients (1811 on *VESIcare* and 1216 on placebo), and approximately 90% of these patients completed the 12-week studies.[1,17] The majority of patients were Caucasian (93%)

and female (80%) with a mean age of 58 years. In addition to the placebo arm which was included in all studies, two of the four studies evaluated *VESIcare* 5 mg and 10 mg and the other two evaluated *VESIcare* 10 mg; one also included tolterodine 2 mg twice daily as an active treatment arm, but no formal statistical comparisons were performed between the active treatment arms and this arm was not included in the pooled analysis. [59]

The primary endpoint in all four trials was the mean change from baseline to 12 weeks in number of micturitions/24 hours.[1,17] Secondary endpoints included mean change from baseline to 12 weeks in number of incontinence episodes/24 hours, mean volume voided per micturition, mean change from baseline in number of urgency episodes/24 hours and mean change from baseline in number of nocturnal voids/24 hours. All efficacy variables were based on information collected via patient diaries, which were completed for the 3 days immediately preceding the visits at baseline, week 4, week 8, and week 12.

The safety of *VESIcare* was evaluated on the basis of incidence and severity of adverse events, ECG parameters, laboratory parameters (including hematology, biochemistry, urinalysis and urine culture), vital signs, and post-void residual volume.[18]

Efficacy Results

The protocols for these four pivotal studies were similar, which allowed for the pooling of results.[17,63]. The mean change in the number of micturitions per 24 hours was significantly greater with *VESIcare* 5 mg (-2.3; $P < 0.001$) and *VESIcare* 10 mg (-2.7; $P < 0.001$) compared to placebo, (-1.4). [1] The mean change in the number of incontinence episodes per 24 hours was significantly greater with *VESIcare* 5 mg (-1.5; $P < 0.001$) and *VESIcare* 10 mg (-1.8; $P < 0.001$) treatment groups compared to placebo (-1.1). A total of 781 (68%) in the placebo group, 314 (56%) receiving *VESIcare* 5 mg, and 778 (67%) patients receiving *VESIcare* 10 mg reported incontinence at baseline.[64] At study endpoint, 51% and 52% of patients who reported incontinence episodes at baseline and who received *VESIcare* 5 mg and *VESIcare* 10 mg, respectively, reported no incontinence episodes based on a 3-day patient diary, compared with 34% of patients who received placebo ($P < 0.001$ vs placebo for both treatment groups).[63] The mean increase in the volume voided per micturition was significantly greater with *VESIcare* 5 mg (32.3 mL; $P < 0.001$) and *VESIcare* 10 mg (42.5 mL; $P < 0.001$) compared with placebo (8.5 mL).

Additional results from the four pooled studies are presented in Table 20.[17]

Table 20. Mean/Median Change from Baseline to Endpoint for VESIcare 5 mg and 10 mg and Placebo for Pooled Pivotal Studies[17,63]

Parameter	**Placebo**		***VESIcare* 5mg‡**		***VESIcare* 10mg‡**	
	Mean	**Median**	**Mean**	**Median**	**Mean**	**Median**
Urinary Frequency (Number of Micturitions/24 hours)*						
	(N = 1138)		(N = 552)		(N = 1158)	
Baseline	11.9	11	12.1	11	11.9	11
Reduction	1.4	1.3	2.3	2	2.7	2.3
% reduction	10.6	12	18.3	19.4	21.5	22.5
P value vs. placebo			<0.001		<0.001	
Number of Incontinence Episodes/24 hours†						
	(N = 781)		(N = 314)		(N = 778)	
Baseline	2.9	2	2.6	2	2.9	2
Reduction	1.1	0.7	1.5	1	1.8	1.3
% reduction	31.6	63.6	60.1	100	59.8	100
P value vs. placebo			<0.001		<0.001	
Volume Voided per micturition [mL]†						
	(N = 1135)		(N = 552)		(N = 1156)	
Baseline	165.5	153.8	149	138.9	163.4	154.9
Increase	8.5	4.3	32.3	27.1	42.5	38.1
% increase	9	3.1	25.2	19	31.5	25.7
P value vs. placebo			<0.001		<0.001	
Number of Urgency Episodes/24 hours†						

*Primary endpoint; †Secondary endpoint; ‡Treatment group comparisons between *VESIcare* and placebo are presented for actual mean change from baseline.

Parameter	**Placebo**		***VESIcare* 5mg‡**		***VESIcare* 10mg‡**	
	Mean	**Median**	**Mean**	**Median**	**Mean**	**Median**
	(N = 1124)		(N = 548)		(N =1151)	
Baseline	6.3	5.7	5.9	4.3	6.2	5.3
Reduction	2	1.7	2.9	2.3	3.4	2.7
% reduction	30.5	40	51.7	66.1	52.4	70
P value vs. placebo			<0.001		<0.001	
Number of nocturnal voids/24 hours†						
	(N = 1062)		(N = 514)		(N = 1082)	
Baseline	2.2	2	2.2	2	2.1	2
Reduction	0.5	0.3	0.6	0.7	0.6	0.7
% reduction	12.7	25	24.2	33.3	25.7	33.3
P value vs. placebo			<0.05		<0.01	
Nocturia Episodes/24 hours†						
	(N = 1005)		(N = 494)		(N = 1035)	
Baseline	1.8	1.7	2	1.7	1.8	1.7
Reduction	0.4	0.3	0.6	0.7	0.6	0.7
% Reduction	11.8	25	23.6	35.5	28.8	36.4
P value vs. placebo			<0.05		<0.001	
*Primary endpoint; †Secondary endpoint; ‡Treatment group comparisons between *VESIcare* and placebo are presented for actual mean change from baseline.						

Safety Results

The safety population for the four pooled studies included a total of 3027 patients (1216 placebo, 578 *VESIcare* 5 mg, 1233 *VESIcare* 10 mg). The percentages of patients with treatment-emergent adverse events exceeding placebo rate and reported by 1% or more patients for combined pivotal studies are provided in Table 3.[65] In both groups, the most common reason for discontinuation was due to adverse events (5.4% for placebo, 3.6% for *VESIcare* 5 mg and 6.9% for *VESIcare* 10 mg). The most frequent reason for discontinuation due to an adverse event was dry mouth (1.5%).

Analysis of routine clinical laboratory parameters indicated no evidence of influence of *VESIcare* on hematology analytes, clinical chemistry analytes, or urinalysis parameters. Analysis of vital signs data showed no evidence of influence of *VESIcare* on systolic blood pressure, diastolic blood pressure, or pulse rate.

Long Term Safety and Efficacy Study

Open-Label, Long-Term Study

All patients completing the two pivotal studies that evaluated the efficacy, safety, and tolerability of *VESIcare* 5 mg and 10 mg once daily were eligible to enter an open-label, long-term, extension study. [22] The objectives of the study were to evaluate safety and tolerability, and secondarily to assess efficacy. A total of 91% (1637/1802) of patients who completed the two 12-week studies chose to participate in the extension study. All patients who entered the open-label phase received *VESIcare* 5 mg for the first 4 weeks. Dose changes were allowed, in consultation with the investigator, at 12-week intervals. A total of 81% (1329/1633) of the enrolled patients completed the additional open-label, 40-week treatment period. A total of 685 patients (42%) received *VESIcare* 5 mg throughout the open-label extension, 840 patients (51%) chose to increase their dose to *VESIcare* 10 mg for the remainder of the study, and 108 patients (7%) increased their dose to 10 mg, but chose to decrease it back to 5 mg by the end of the study.

Safety and Tolerability

The favorable safety and tolerability of *VESIcare* observed during the initial 12-weeks of treatment appeared to be maintained during the additional open-label, 40-week period. The most commonly reported adverse events were dry mouth, constipation and blurred vision. [22,66] Dry mouth was reported in 10.2% of patients receiving *VESIcare* 5 mg and in 17.4% of patients receiving *VESIcare* 10 mg. Constipation was reported in 4.9% of patients receiving *VESIcare* 5 mg and in 7.9% of patients receiving *VESIcare* 10 mg. Blurred vision was reported in 4.1% of patients receiving *VESIcare* 5 mg and in 4.4% of patients receiving *VESIcare* 10 mg.

Efficacy

The 40-week extension study evaluated mean reductions in number of urgency episodes, number of incontinence episodes, and number of micturitions per 24 hours, in addition to mean increases in volume voided per micturition [22]. Improvements in OAB symptoms observed during the initial 12 weeks of treatment with *VESIcare* appeared to be maintained during the additional open-label 40-week period (Table 21).

Table 21. Mean/Median Changes in Efficacy Parameters for Patients Treated with *VESIcare* During Double-Blind Studies and Open-Label Study [22]

Efficacy Outcome	Baseline from Double-Blind Studies	Endpoint from Double-Blind Studies (after 12 weeks)	Endpoint from Open-Label Study (after 52 weeks)	Overall Change from Original Baseline to Open-Label Study Endpoint
Number of Micturitions/24 hours				
Mean	12.16	9.47	9.18	23% (-2.97)
Median	11.33	8.67	8.33	26% (-3)
Number of Incontinence Episodes/24 hours				
Mean	2.66	1.06	0.93	66% (-1.74)
Median	2	0	0	100% (-1.33)
Volume Voided per Micturition [mL]				
Mean	147.6	183.6	187.4	31% (39.8)
Median	138.8	175.8	177.5	24% (34)
Number of Urgency Episodes/24 hours				
Mean	5.76	2.69	2.28	63% (-3.48)
Median	4.33	1.33	1	82% (-2.67)

Furthermore, other measures of response were maintained or improved throughout the 40-week extension study (Table 22) [22]

Table 22. Percent of Patients Experiencing a Response Who Had Received *VESIcare* During Both Double-Blind and Extention Studies [22]

Response Outcome	Double-Blind Studies Endpoint (%)	Open-Label Study Endpoint (%)
Patients Achieving Continence	52%	58%
Patients Reporting No Urgency	31%	40%
Patients with Normalized Micturition Frequency (< 8 voids/day)	34%	39%

Post-Hoc Analysis in Elderly Patients

Post-Hoc Analysis of Elderly Patients from Pivotal Studies

The protocols for these four pivotal studies were similar, which allowed for the pooling of results. A post-hoc analysis of pooled data from these studies was performed to evaluate the efficacy and tolerability of *VESIcare* in patients ≥ 65 years of age (N = 1,045).[67] The average age of these patients was 71.9 years and 75% were female.

The results demonstrated that treatment with *VESIcare* 5 mg and 10 mg once daily was associated with statistically significant reductions compared to placebo in micturitions, incontinence episodes, volume voided, and urgency episodes in patients ≥ 65 years of age (Table 23). In patients ≥ 65 years who were incontinent at baseline, 49.1% of patients taking *VESIcare* 5 mg and 47.3% of patients taking *VESIcare* 10 mg reported no incontinence episodes at the end of the study compared to 28.9% of patients taking placebo ($P < 0.001$).

Table 23. Mean Changes from Baseline to Endpoint for *VESIcare* in Efficacy Outcomes from Pooled Pivotal Studies in Patients ≥ 65 Years[67]

	***VESIcare* 5 mg**	***VESIcare* 10 mg**	**Placebo**
Number of micturitions/24 hours	n = 182	n = 402	n = 396
Mean baseline value	11.7	11.6	11.6
Mean change from baseline	-2.0*	-2.5*	-1.1
Number of incontinence episodes/24 hours	n = 106	n = 296	n = 287
Mean baseline value	2.5	3.0	3.0
Mean change from baseline	-1.5†	-1.9*	-1.0
Volume voided per micturition (mL)	n = 182	n = 401	n = 396
Mean baseline value	147.0	158.0	162.6
Mean change from baseline	30.2*	46.2*	9.1
Number of urgency episodes/24 hours	n = 182	n = 398	n = 391
Mean baseline value	5.9	6.0	6.2
Mean change from baseline	-3.2*	-3.2*	-1.6
*$P < 0.001$ vs. placebo; †$P = 0.013$ vs. placebo			

Post-Hoc Analysis of Elderly Patients from Open-Label Study

A post-hoc analysis was also conducted using data from the 40-week, open-label, long-term, extension study to evaluate the safety and efficacy of *VESIcare* in patients ≥ 65 years of age. The 40-week extension study evaluated micturitions per 24 hours, incontinence episodes per 24 hours, volume voided per micturition and urgency episodes per 24 hours.[67] [22] Improvements in OAB symptoms observed during the initial 12 weeks of treatment with *VESIcare* appeared to be maintained during the additional open-label, 40-week period. Table 24 presents mean and median changes from baseline to endpoint in efficacy outcomes for patients ≥ 65 years from the post-hoc analysis. The completion rate in patients ≥ 65 years (80%) was similar to the completion rate in patients ≥ 18 years (81%) for the open-label, extension study. Statistical comparisons have not been conducted between these groups. In patients ≥ 65 years incontinent at baseline, 59.5% of patients taking solifenacin 5 mg or solifenacin 10 mg during the 12-week, double-blind trials and open-label, extension study reported no incontinence episodes at the end of the open-label, extension study.

Table 24. Mean/Median Changes in Efficacy Parameters for Patients ≥ 65 Years Treated with *VESIcare* During Double-Blind Studies and Open-Label Study[67]

Efficacy Outcome	Baseline from Double-Blind Studies	Endpoint from Double-Blind Studies (after 12 weeks)	Endpoint from Open-Label Study (after 52 weeks)	Overall Change from Original Baseline to Open-Label Study Endpoint
Number of Micturitions/24 hours				
Mean	11.65	9.25	9.09	22% (-2.56)
Median	11.00	8.67	8.67	21% (-2.33)
Number of Incontinence Episodes/24 hours				
Mean	2.75	1.19	0.96	65% (-1.79)
Median	2.00	0.33	0	66% (-1.33)
Volume Voided per Micturition (mL)				
Mean	146.20	183.78	181.56	24% (35.30)
Median	139.80	180.00	175.20	23% (32.73)
Number of Urgency Episodes/24 hours				
Mean	5.65	2.55	2.37	67% (-3.28)
Median	4.00	1.00	1.00	58% (-2.67)

Safety Results in Elderly Patients

The most common adverse events reported in elderly patients treated with *VESIcare* in double-blind, pivotal trials and the open-label, extension study were dry mouth, constipation, and urinary tract infection (Table 25).[67] Discontinuation rates due to all adverse events in elderly patients from double-blind, pivotal studies were *VESIcare* 5 mg (4.7%), *VESIcare* 10 mg (9.3%), and placebo (5.5%). About 9.2% of patients discontinued *VESIcare* in the open-label, extension trial due to an adverse event.

Table 25. Most Commonly Reported Treatment-Emergent Adverse Event Rates with *VESIcare* in Elderly Patients, from Pivotal Studies[67]

Adverse Event	Pivotal Studies			Open-Label, Extension Study	
	VESIcare 5 mg	*VESIcare* 10 mg	Placebo	*VESIcare* 5 mg	*VESIcare* 10 mg
	n = 192	n = 431	n = 422	n = 509	n = 330
Dry Mouth	13.5%	31.6%	4.7%	13.6%	21.5%
Constipation	9.4%	18.1%	4.3%	6.1%	11.5%
Urinary Tract Infection	3.6%	7.0%	3.1%	5.7%	7.0%

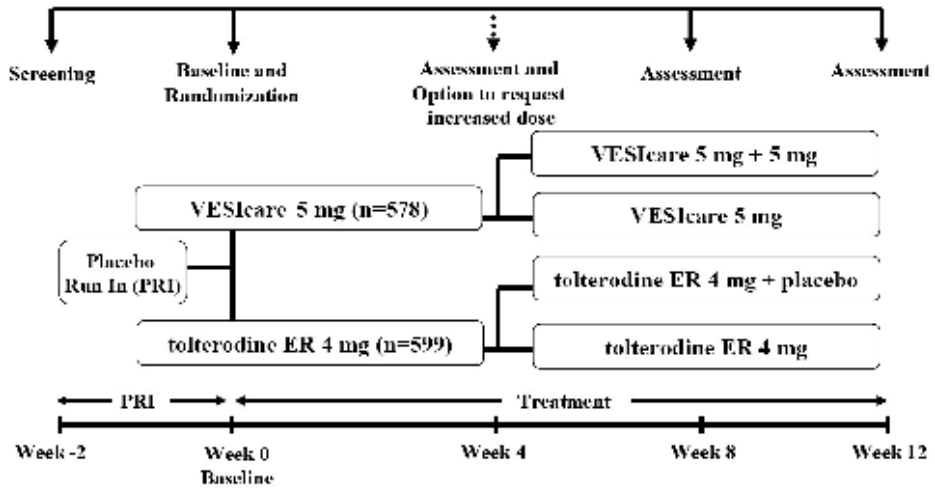
STAR Study

Study Design

Solifenacin in a flexible-dose regimen with Tolterodine extended release (ER) as an Active comparator in a Randomized (STAR) trial was conducted in 17 European and Eastern European countries.[30,68] The study population consisted of male and female patients aged ≥18 years with symptoms of overactive bladder (OAB) for ≥3 months. In addition, patients had to have a mean micturition frequency of ≥8 per 24 hours during the 3-day micturition diary period. Patients also had to experience at least one of the following symptoms during the 3-day micturition diary period: at least three urinary incontinence episodes or at least three urgency episodes.

This was a 12-week double-blind, double-dummy, parallel arm trial in which patients with OAB were randomized, after a 2-week placebo run-in, to receive either *VESIcare* 5 mg once daily or tolterodine 4 mg ER once daily (European formulation) (Figure 2). Throughout the study, all patients received two tablets and one capsule to maintain blinding. Tolterodine ER or equivalent placebo was blinded by an over-encapsulation process. After 4 weeks of treatment with *VESIcare* 5 mg or tolterodine ER 4 mg, patients were able to request a medication dose increase. At that point, patients receiving *VESIcare* 5 mg who requested a dose increase received an additional *VESIcare* 5 mg tablet (total of 10 mg once daily, consistent with approved product labeling); patients receiving tolterodine ER 4 mg continued on the tolterodine ER dose along with placebo (consistent with approved product labeling).

Figure 2. STAR Study Design [68]



The primary objective of the study was to assess the efficacy of a flexible-dose regimen of *VESIcare* 5 mg or 10 mg once daily compared with tolterodine 4 mg ER once daily in patients with OAB.[30,68] Secondary objectives were to assess the safety and tolerability of *VESIcare* and tolterodine ER and to determine the percentage of patients who requested a medication dose increase beyond their starting dose.

The primary efficacy endpoint was to establish noninferiority of *VESIcare* compared with tolterodine ER based on the mean change from baseline to endpoint in the number of micturitions/24 hours. Secondary efficacy endpoints, evaluated as superiority comparisons, included the percentage of incontinent patients reporting no incontinence episodes at endpoint, mean change from baseline to endpoint in the number of incontinence episodes, urge incontinence episodes, pads used, urgency episodes, volume voided per micturition, nocturia episodes and patient perception of bladder condition (PBC). All efficacy variables were based on information collected via 3-day patient diaries, which were completed for the 3 days immediately preceding the visits at baseline and weeks 4, 8, and 12. The patients recorded micturitions, incontinence episodes, urge incontinence episodes, pads used, the volume voided per micturition and urgency episodes. For these endpoints, symptoms were recorded daily during the 3-day period with the exception of volume voided per micturition which was recorded during any 2 of the 3 days. When recording micturitions, patients also filled out a check box indicating whether or not the episode disturbed the patient's sleep, indicating a nocturia episode.

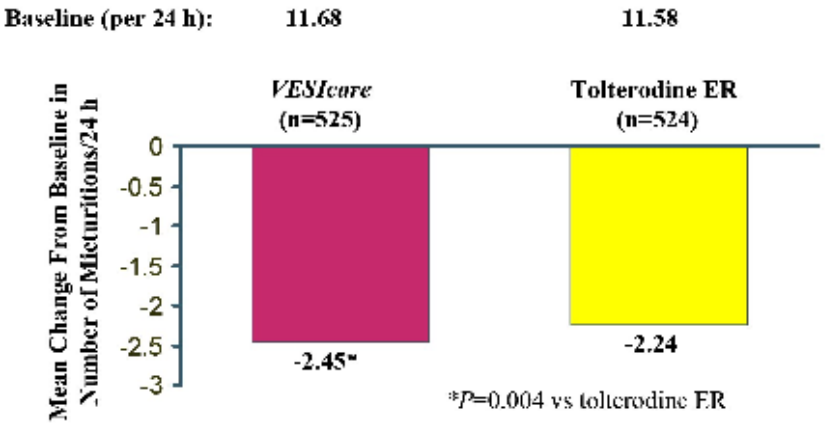
The patient PBC was assessed using a validated 6-point categorical scale [69]. The categorical scale included the following responses to: "My bladder condition…" 1) does not cause me any problems at all; 2) causes me some very minor problems; 3) causes me some minor problems; 4) causes me some moderate problems; 5) causes me severe problems or 6) causes me many severe problems. In addition, the patient assessment of treatment benefit and the physician assessment of treatment benefit were reported for descriptive purposes.[30,68] Safety assessments included incidence and severity of adverse events.

Demographic characteristics were similar for the two treatment arms, with the majority of patients being female (approximately 87%) and Caucasian (99.5%) and patients had a mean age of approximately 57 years. The study patient populations included the full analysis set (FAS) defined as all patients who were randomized, took at least one dose of double-blind study medication, provided efficacy data at baseline and during double-blind treatment . The FAS was comprised of 1177 randomized patients with a total of 578 patients randomized to receive *VESIcare* 5 mg and 599 patients randomized to receive tolterodine ER 4 mg. The per protocol set (PPS) was defined as all patients in the FAS population who completed the study without major deviations from the protocol and who had valid diary data at week 12. The safety population was defined as all patients who were randomized and took at least one dose of double-blind study medication.

Efficacy Results

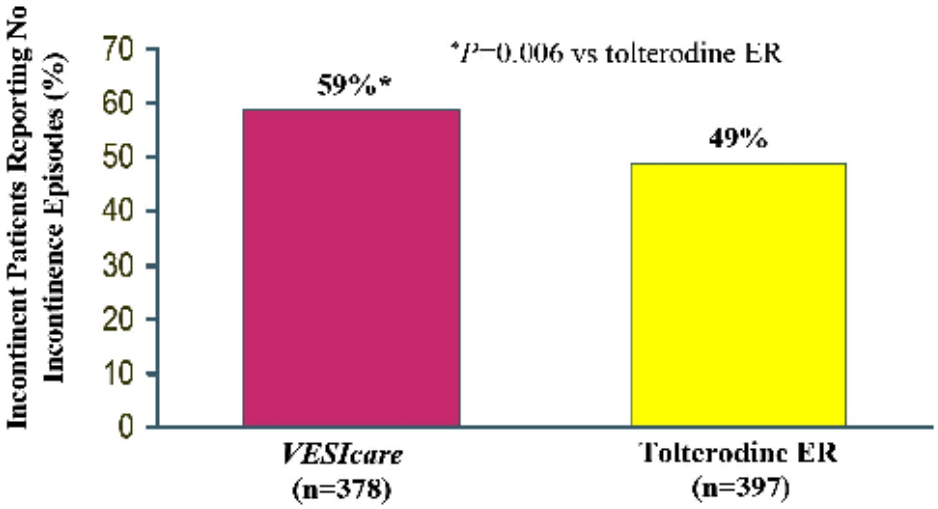
VESIcare was found to be noninferior to tolterodine ER for mean change from baseline in micturition frequency (PPS) (P = 0.004, 95% Confidence Interval: -0.48, 0.10) (Figure 3).

Figure 3. Mean Change from Baseline to Endpoint for Micturition Frequency for *VESIcare* and Tolterodine ER (PPS)[30,68]



Of those patients reporting incontinence at baseline, the comparison of the percentage of incontinent patients reporting no incontinence episodes at endpoint as measured by the 3-day patient diary was statistically significant in favor of *VESIcare*: 59% compared with 49% of patients treated with tolterodine ER (FAS; P = 0.006) (Figure 4). [30,68]

Figure 4. Incontinent Patients Reporting No Incontinence Episodes at Endpoint for *VESIcare* and Tolterodine ER (FAS) [30,68]



Additional secondary endpoints are presented inTable 26.

Table 26. Mean Changes from Baseline to Endpoint for *VESIcare* and Tolterodine ER on Additional Secondary Endpoints (FAS)[30,68]

Endpoint	*VESIcare* 5 mg or 10 mg	Tolterodine ER 4 mg
Number of Incontinence Episodes/24 hours*		
Mean Baseline	2.77	2.55
Mean Reduction	1.6	1.11
P value, *VESIcare* vs. tolterodine ER	0.006†	
Number of Urge Incontinence Episodes/24 hours*		
Mean Baseline	2.31	2.12
Mean Reduction	1.42	0.83
P value, *VESIcare* vs. tolterodine ER	0.001†	
Number of Pads Used/24 hours*		
Mean Baseline	3.25	2.93
Mean Reduction	1.72	1.19
P value, vs. *VESIcare* vs. tolterodine ER	0.002†	
Number of Urgency Episodes/24 hours*		
Mean Baseline	6.01	5.84
Mean Reduction	2.85	2.42
P value, *VESIcare* vs. tolterodine ER 4 mg	0.035†	
Volume Voided per Micturition [mL]*		
Mean Baseline	146.84	145.14
Mean Increase	37.95	31
P value, *VESIcare* vs. tolterodine ER	0.010†	
Number of Nocturia Episodes/24 hours*		
Mean Baseline	2.02	1.92
Mean Reduction	0.71	0.63
P value, vs. *VESIcare* vs. tolterodine ER	0.73	
Patient Perception of Bladder Condition*		
Mean Baseline	4.43	4.45
Mean Reduction	1.51	1.33
P value, vs. *VESIcare* vs. tolterodine ER	0.006†	
Patient Assessment of Treatment Benefit‡		
No Benefit	10.50%	15.20%
A Little Benefit	34.60%	40.90%
Very Much Benefit	55.00%	43.90%
Physician Assessment of Treatment Benefit‡		

*Secondary endpoint, superiority comparison (FAS)

†Statistically significant vs. tolterodine ER

‡Descriptive statistics

Endpoint	***VESIcare*** **5 mg or 10 mg**	**Tolterodine ER 4 mg**
No Benefit	10.90%	14.40%
A Little Benefit	33.90%	40.60%
Very Much Benefit	55.20%	45.00%
*Secondary endpoint, superiority comparison (FAS) †Statistically significant vs. tolterodine ER ‡Descriptive statistics		

After week 4 of treatment in the study, 48% of patients receiving *VESIcare* 5 mg requested a dose increase in consultation with a physician, and began receiving *VESIcare* 10 mg once daily (consistent with approved product labeling).[30,68] A total of 51% of patients in the tolterodine ER 4 mg arm requested a dose increase in consultation with a physician; patients in this group received tolterodine ER 4 mg plus placebo once daily (consistent with approved product labeling).

Safety Results

The most commonly reported treatment-emergent adverse events were dry mouth, constipation and headache (Table 27).[30,68]. The majority of adverse events were mild to moderate. In regards to dry mouth, mild dry mouth was reported by 17.5% and 14.8% of patients for *VESIcare* and tolterodine ER, respectively. Moderate dry mouth was reported by 10.8% and 7.7% of patients for *VESIcare* and tolterodine ER, respectively, and severe dry mouth reported by 1.7% and 1.5% of patients for *VESIcare* and tolterodine ER, respectively. Overall, 3.5% of patients treated with *VESIcare* and 3.0% of patients treated with tolterodine ER discontinued therapy due to adverse events [30,68]

Table 27. Incidence of Treatment-Emergent Adverse Events Reported by ≥2% of Patients*[68]

Adverse event	***VESIcare*** **5 mg or 10 mg n = 593**	**Tolterodine ER 4 mg n = 607**
Dry mouth	30.00%	24.10%
Constipation	6.40%	2.50%
Headache	2.70%	3.60%
*Safety Population		

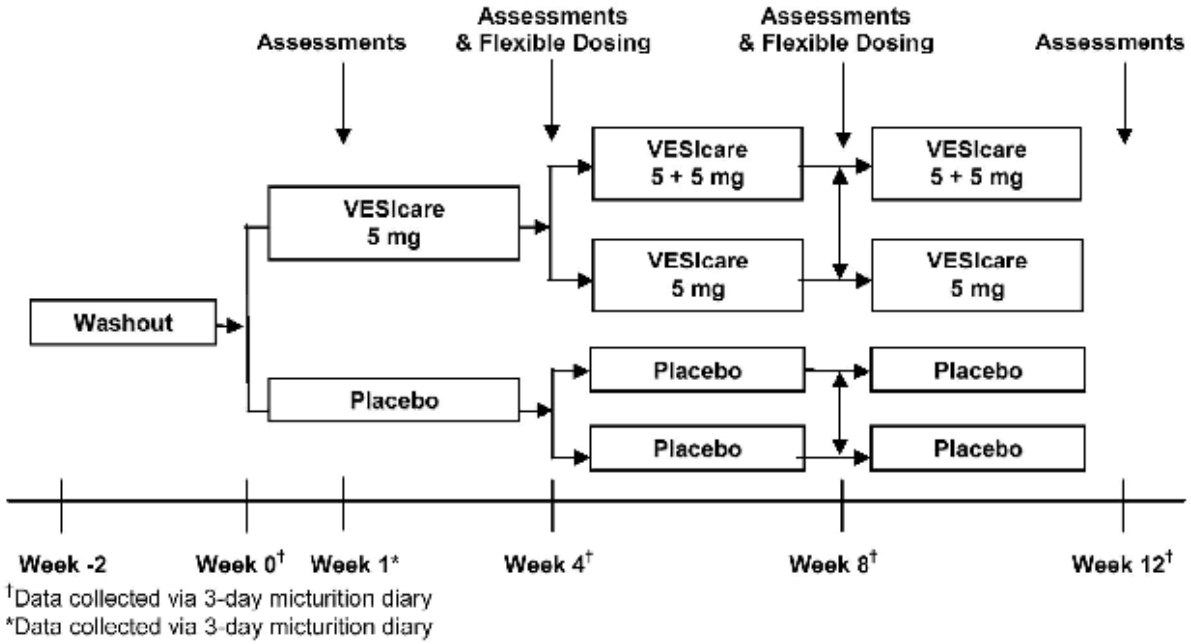
VENUS Study

Study Design

The ***VESIcare*** **E**fficacy and safety in patie**N**ts with **U**rgency **S**tudy (VENUS) was a 12-week, prospective, multicenter, randomized, placebo-controlled, double-blind trial conducted to assess the use of *VESIcare* in patients with urgency associated with overactive bladder (OAB).[70,71] The study population (N=739) consisted of male and female patients aged ≥ 18 years with symptoms of OAB for ≥ 3 months. Patients included in the study were either treatment naïve or previously treated with anticholinergic agents for OAB. Patients had an average of at least one urinary urgency episode (with or without urge incontinence) per 24 hours and ≥ 8 episodes of micturition frequency and/or nocturia per 24 hours during the screening period.

After a 2-week washout, patients were randomized to receive either *VESIcare* 5 mg or placebo once daily. After 4 weeks of treatment with *VESIcare* 5 mg, patients were able to maintain their dose or request a medication dose increase. At week 8, patients were able to maintain their dose, request a dose increase to 10 mg, or request a dose decrease to 5 mg (Figure 5). Patients receiving placebo were able to request a change in dose similar to those receiving *VESIcare*, only their drug remained placebo.

Figure 5. VENUS Study Design[71]



The primary objective of the study was to evaluate the efficacy of *VESIcare* 5 mg and 10 mg in patients with urgency-associated OAB. The primary efficacy variable was the mean change from baseline to end of study in the number of urgency episodes/24 h.

Secondary efficacy variables included median change from baseline to end of study in Warning Time, and mean change from baseline to end of study in the Indevus Urgency Severity Scale (IUSS) and the Urgency Perception Scale (UPS).

Additional secondary endpoints included mean change from baseline in micturition frequency/24 h, incontinence episodes/24 h, nocturia episodes/24 h, and nocturnal voids/24 h. Efficacy variables were based on information collected via 3-day patient diaries, which were completed for the 3 days immediately preceding each study visit. Prior to Week 1, patients completed a 7-day diary. Safety assessments included incidence and severity of adverse events.

Demographic characteristics were similar for the two treatment arms, with the majority of patients being female (approximately 84.2%) and Caucasian (83.5%). Patients had a mean age of 57 years.

Efficacy Results

Dose Changes

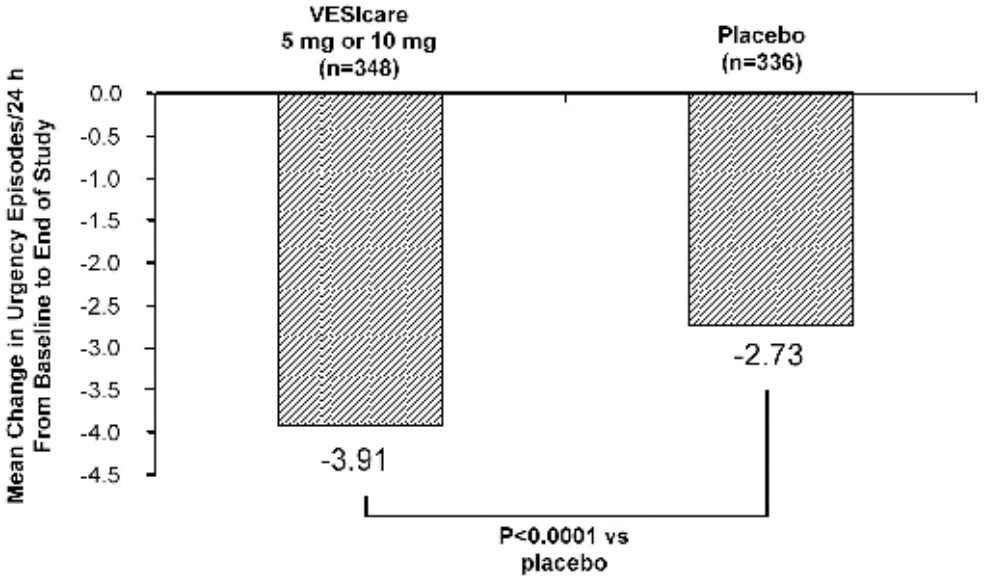
At week 4 of the study, 164 (44.1%) patients receiving *VESIcare* 5 mg and 216 (58.9%) patients receiving placebo increased their dose to *VESIcare* 10 mg or matching placebo, respectively.[70,71] At Week 8 of the study, 23 of the 164 patients on *VESIcare* 10 mg decreased their dose to *VESIcare* 5 mg and 28 of the 176 patients on *VESIcare* 5 mg increased their dose to *VESIcare* 10 mg. All dose changes were made in consultation with a physician.

Primary Endpoint

Urgency Episodes

At baseline, patients reported 6.15 and 6.03 urgency episodes/24 h for *VESIcare* and placebo, respectively. Patients treated with *VESIcare* reported a significantly greater reduction in urgency episodes/24 h from baseline to end of study compared to patients treated with placebo ($P<0.0001$) (Figure 6).

Figure 6. Mean Change from Baseline to End of Study in Urgency Episodes/24 h for *VESIcare* and Placebo[71]



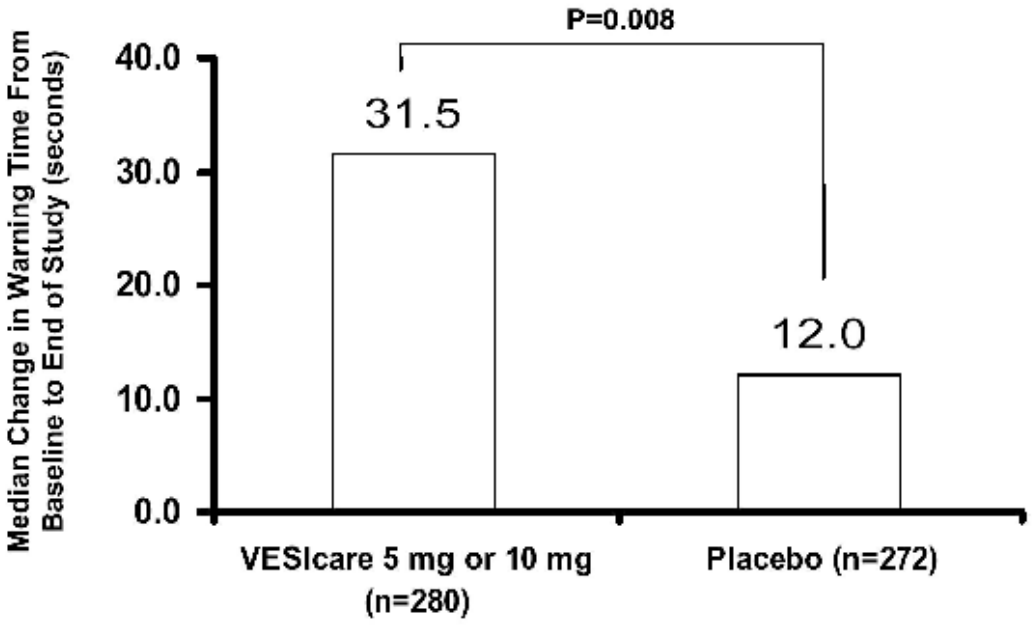
Secondary Endpoints

Warning Time

Warning time was defined as the time from the first sensation of urgency to voiding. Patients were given a stopwatch and a Warning Time Record to document warning times. Warning time was documented by each patient 1 day before he/she records 3-day diary data prior to Visits 2 (week 0/baseline) and 6 (week 12). The following directions were provided: Start the stop watch at the first sensation of urgency. Stop the watch when you begin to void; record the time on the record.

At baseline, patients reported a median warning time of 67.8 seconds and 65.0 seconds in the *VESIcare* and placebo groups, respectively. At the end of study, patients treated with *VESIcare* reported a significantly greater increase in warning time compared to patients treated with placebo (P=0.008) (Figure 7).

Figure 7. Median Change from Baseline to End of Study in Warning Time for *VESIcare* and Placebo



Indevus Urgency Severity Scale (IUSS)

The IUSS is a validated single-item four-point scale used to measure the severity of urgency associated with OAB (0=no urgency to 3=severe, extreme urgency). At baseline, patients in both treatment groups reported a mean IUSS score of 2.0. At the end of study, patients treated with *VESIcare* reported a greater change in the mean IUSS score (-0.9) compared to patients treated with placebo (-0.5) (P<0.0001).

Urgency Perception Scale (UPS)

The UPS is a validated three-point scale used to measure the patient perception of urgency. Responses can range from 1 (usually not able to hold urine) to 3 (usually able to finish a task before going to the bathroom). At baseline, the mean UPS score was 2.0 for both treatment groups. At the end of study, patients treated with *VESIcare* reported a greater change in the mean UPS score (0.4) compared to patients treated with placebo (0.2) (P=0.0018).

Additional Secondary Endpoints

Compared with placebo, patients treated with *VESIcare* reported significantly greater changes from baseline to end of study in micturition frequency/24 h (P=0.0014) and incontinence episodes/24 h (P<0.0001). There was no statistical difference between treatment groups in the reduction of nocturia episodes or nocturnal voids.

Safety Results

The most commonly reported treatment-related adverse events were dry mouth, constipation, blurred vision, dizziness, and fatigue (Table 28). Treatment-related adverse events were defined as those reported by ≥2% of patients treated with *VESIcare* and ≥1% over placebo value. Overall, 6.5% of patients treated with *VESIcare* and 4.6% of patients treated with placebo discontinued therapy due to adverse events.

Table 28. Incidence of Treatment-Related Adverse Events Reported*[71]

Adverse event	*VESIcare* 5 mg or 10 mg n = 372	Placebo n = 367
Dry mouth	25.30%	9.00%
Constipation	14.80%	9.30%
Blurred vision	3.80%	1.10%
Dizziness	3.20%	1.90%
Fatigue	2.70%	1.10%
* Safety Population		

2.2 Evidence Table for Key Clinical Studies

Table 29. - See Appendix

2.3 Outcomes Studies and Economic Evaluation

VERSUS Study

Study Design

VERSUS (*VESIcare* Efficacy and Research Study US) was a 12-week, prospective, non-randomized, open-label, flexible-dose, multicenter study which assessed the efficacy and safety of *VESIcare* 5 or 10 mg in patients wishing to switch from tolterodine extended release (ER) due to dissatisfaction with urgency episode improvement.[72,73] The study population (N = 441) consisted of male and female patients ≥ 18 years with overactive bladder (OAB) for 3 months or longer and an average of at least 3 urgency episodes/24 hours while taking tolterodine ER. All patients received tolterodine ER for at least 4 weeks prior to study entry.

After a 2-week washout period, all patients were started on *VESIcare* 5 mg once daily. After 4 weeks of treatment with *VESIcare*, patients were able to maintain their dose or request a dose increase to 10 mg. After 8 weeks of treatment with *VESIcare*, patients were able to maintain their dose or request a dose decrease to 5 mg. Patients received a total of 12 weeks of treatment with *VESIcare*.

The primary efficacy outcome was the mean change from pre-washout to endpoint in the number of urgency episodes/24 hours. Secondary outcomes included mean change from pre-washout to endpoint in micturition frequency/24 hours, incontinence episodes/24 hours, nocturia episodes/24 hours, nocturnal voids/24 hours, Patient Perception of Bladder Condition (PPBC) score, and Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire (OAB-q) score. The PPBC requires patients to answer questions about their bladder symptoms using the following, validated, 6-point, categorical scale: 1) does not cause me any problems at all; 2) causes me some very minor problems; 3) causes me some minor problems; 4) causes me (some) moderate problems; 5) causes me severe problems; 6) causes me many severe problems.[74] The OAB-q is a validated, patient-administered, 33-item questionnaire consisting of 6 subscales including bother, coping, concern, sleep, social interaction, and health-related quality of life. [75] Patients rated each item on a 6-point Likert scale.

Economic patient-reported outcomes were prospectively collected as secondary endpoints in this open-label, multicenter study of patients who wished to switch from tolterodine ER to *VESIcare* for the treatment of symptoms of OAB.[56] The three patient-reported questionnaires included the Work Productivity Assessment Index (WPAI), the Medical Care Use Index (MCUI), and the Health Utilities Index Mark 2 and Mark 3 (HUI 2/3).

The WPAI assesses four areas: absenteeism (time missed at work), presenteeism (impairment while at work), work productivity loss (combination of absenteeism and presenteeism), and activity impairment. The MCUI assesses the effect of overactive bladder condition on access to medical services over the past 3 months. Data was collected on the frequency of physician visits related to the bladder condition, urinary tract infections (UTIs), skin rashes, and falls. Furthermore, information on behavioral therapies (timed voiding, fluid management, pelvic floor exercises, biofeedback, and electrical stimulation) was also collected. The HUI 2/3 is a 15-item instrument that describes health status, as it relates to vision, hearing, speech, emotion, pain, ambulation, dexterity, cognition, and self-care. The WPAI, MCUI, and HUI 2/3

were analyzed after 12 weeks of solifenacin treatment and compared to the pre-washout assessments when patients were taking tolterodine extended-release.

Efficacy Results

A total of 441 patients were included in the safety population and the completion rate was 88.4% for this group. The mean age of patients enrolled in the study was 61.4 years and most patients were female (88.2%) and Caucasian (88.9%). Patient demographics were similar between the safety population and full analysis set (FAS). Compared to pre-washout, the primary outcome, mean number of urgency episodes/24 hours, improved significantly with *VESIcare* ($P < 0.0001$). Secondary outcomes including the number of micturitions/24 hours, incontinence episodes/24 hours, nocturia episodes/24 hours, and noctural voids/24 hours also improved significantly with *VESIcare* compared to pre-washout ($P < 0.0001$). Please see Table 30 for additional information.

Table 30. Mean Changes from Pre-Washout to Endpoint for *VESIcare* in Efficacy Outcomes (FAS)

	Mean Pre-Washout Value	Mean Change
Primary Outcome		
Urgency Episodes/24 Hours (n = 425)	6.03	-3.41*
Secondary Outcomes		
Micturitions/24 Hours (n = 425)	10.59	-1.57*
Incontinence Episodes/24 Hours (n = 306)	3.04	-1.86*
Nocturia Episodes/24 Hours (n = 348)	1.83	-0.72*
Nocturnal Voids/24 Hours (n = 388)	2.32	-0.79*
FAS = Full analysis set; * $P < 0.0001$ for change from pre-washout value to endpoint		

The mean change in PPBC score from pre-washout to endpoint indicated significant improvement in patients' perception of bladder symptoms ($P < 0.0001$). The mean pre-washout PPBC score was 4.2 indicating that, during treatment with tolterodine ER, patients believed their bladder symptoms caused moderate to severe problems. Following open-label treatment with *VESIcare*, the mean endpoint PPBC score was 3.0 indicating patients believed their bladder symptoms caused some minor problems. Each of the 6 OAB-q subscales (bother, coping, concern, sleep, social interaction, and health-related quality of life) improved significantly from pre-washout to endpoint ($P < 0.0001$).

Based on the MCUI data, patients experienced a significant reduction in number of physician visits, frequency of urinary tract infections, and quantity of pads/diapers used weekly from the pre-washout period to Week 12 of *VESIcare* therapy (Table 31). The change in number of skin rashes and number of falls from pre-washout to Week 12 of *VESIcare* therapy did not reach statistical significance.

Table 31. MCUI Key Resource Utilization Findings[76]

Outcome	N	Pre-Washout Mean ± SE	Week 12 Mean ± SE	Change Mean ± SE	P-Value
Number of physician office visits	386	1.24 ± 0.08	0.24 ± 0.04	-1.00 ± 0.08	<0.0001*
Number of UTIs	373	0.22 ± 0.03	0.10 ± 0.02	-0.12 ± 0.03	<0.0001*
Number of pads/diapers used weekly	372	10.66 ± 0.87	7.87 ± 0.81	-2.79 ± 0.83	0.0009*
Number of skin rashes	360	0.61 ± 0.34	0.15 ± 0.06	-0.46 ± 0.34	0.1801
Number of falls	372	0.18 ± 0.04	0.23 ± 0.07	0.04 ± 0.07	0.5561
*P < 0.05 indicates statistical significance					

The use of *VESIcare* resulted in improvements in medical resource utilization over pre-washout (tolterodine ER). *VESIcare* results in an estimated annual cost savings of $362 to $615 per patient year (Table 32).

Table 32. Calculated Resource Cost Savings* (76,77,78)

	Pre-Washout Tolterodine Failures	Annual Tolterodine Failures†	Tolterodine Failure Annual Costs	*VESIcare* 12-week Utilization	*VESIcare* Annual Utilization†	*VESIcare* Annual Costs
Office Visits‡§	1.24	4.96	$313.17	0.24	0.96	$60.61
UTIs‡	0.22	0.88	$530.64	0.10	0.4	$241.20
Pad/Diaper‡	10.66	554.32	$277.16	94.4	409.2	$204.60
Mean Total Annual Costs			$1120.97			$506.41
UTI and Pad Costs Only			$807.80			$445.80

*Estimated Costs from 2005 = $63.14 (office visits), $603 (UTI), $0.50 (Pad/Diaper)

† Annual rates were extrapolated from 12-week data

‡$P < 0.05$

§ The reduction in MD visits may be due to study design

Use of *VESIcare* resulted in improvements in productivity loss over pre-screen (tolterodine ER) in all WPAI outcome assessments (Table 33). The mean change from pre-washout to Week 12 in the Health State Utility Scale (0.01) was not statistically significant. The HUI 2/3 is a summary score including multiple attributes, and some of these attributes (e.g., vision, hearing, speech,) may not be affected by OAB or its treatment.

Table 33. Work and Activity Impairment (WPAI) and Health Utility (HUI) Findings(76)

Outcome	N	Pre-Washout Mean ± SE	Week 12 Mean ± SE	Change Mean ± SE	P-Value*
Percent work missed due to bladder condition	146	2.06 ± 0.56	0.22 ± 0.10	-1.84 ± 0.57	0.0017*
Percent impairment while working due to bladder condition	159	22.89 ± 1.70	11.26 ± 1.01	-11.64 ± 1.64	< 0.0001*
Percent overall work impairment due to bladder condition	146	24.00 ± 1.80	11.85 ± 1.06	-12.14 ± 1.79	< 0.0001*
Percent activity impairment due to problem	408	31.64 ± 1.25	18.43 ± 1.05	-13.21 ± 1.31	< 0.0001*
Health Utilities Index 2/3	397	0.80 ± 0.01	0.81 ± 0.01	0.01 ± 0.01	0.1647

*$P < 0.05$ indicates statistical significance

Safety Results

Most adverse events were anticholinergic in nature and mild-to-moderate in intensity. Treatment-emergent adverse events occurring in > 2% of patients included dry mouth (17.5%), constipation (11.6%), urinary tract infection (4.3%), headache (2.9%), upper respiratory tract infection (2.5%), and blurred vision (2.3%). Approximately 59% of patients experienced at least 1 treatment-emergent adverse event and 3.9% of patients discontinued *VESIcare* due to an adverse event.

Post-Hoc Analysis in Elderly Patients

A post-hoc analysis using data from the VERSUS study was conducted to assess the effect of *VESIcare* on patient-reported economic outcomes in elderly patients.(79) A total of 108 patients 65 to 74 years old

and 86 patients 75 years of age or older met criteria for this analysis. Elderly patients showed significant improvement on all OAB-q subscales ($P < 0.0001$) from pre-washout to endpoint with *VESIcare* treatment. On the WPAI, patients in both age groups showed a significant decrease in activity impairment between pre-washout and endpoint ($P < 0.05$). Few elderly patients were working, however, patients aged 65-74 years who were working (n = 23) reported a significant reduction in impairment while working ($P < 0.05$). Other components of the WPAI (work time missed, work productivity loss) were statistically similar between pre-washout and endpoint. The HUI score was statistically similar from pre-washout to endpoint in both age groups. On the MCUI, patients 65-74 years required 0.95 fewer physician office visits and patients 75 or older required 0.73 fewer physician office visits during the study period compared with the pre-washout period ($P \leq 0.0001$). Pad/diaper use was significantly reduced in patients 65-74 years (mean change: -5.15/week, $P = 0.0174$) , but not in patients ≥75 years. UTIs, skin rashes, falls, and behavioral therapy strategies used were statistically similar in both groups from pre-washout to endpoint.

VOLT Study

The *VESIcare* Open-Label Trial, or VOLT Study, was a prospective, multicenter study evaluating the efficacy of *VESIcare* 5 mg and 10 mg, in a flexible-dosing regimen, conducted in patients with symptoms of OAB.[80,81,82] The study consisted of a 12-week treatment phase followed by an optional 24-week extension phase, although efficacy was evaluated only during the initial 12 weeks of treatment. Patients were treated with *VESIcare* 5 mg initially, with the option to maintain the 5 mg dose or increase to 10 mg at week 4. Patient doses were also evaluated at week 8, where the dose could be maintained, increased to 10 mg or decreased to 5 mg.

The primary efficacy endpoint was to assess the efficacy of *VESIcare* 5 mg and 10 mg based on the mean change from baseline to endpoint in patients' perception of OAB symptoms, using the patient perception of bladder condition (PBC) scale and a visual analog scale (VAS). Secondary endpoints included the most bothersome symptom, the percentage of subjects satisfied and the OAB-questionnaire (OAB-q). The patient PBC was assessed using a validated 6-point categorical scale. The categorical scale included the following responses to: "My bladder condition…" 1) does not cause me any problems at all; 2) causes me some very minor problems; 3) causes me some minor problems; 4) causes me some moderate problems; 5) causes me severe problems or 6) causes me many severe problems. The VAS allowed patients to indicate the presence and degree to which they were bothered by OAB symptoms as measured in mm on a horizontal scale ranging from 0 mm (not at all) to 100 mm (greatly). The OAB-q is a validated, patient-administered tool designed to evaluate quality of life. The safety of *VESIcare* was also assessed.

The study population consisted of men and women ≥ 18 years with overactive bladder symptoms (including urinary frequency, urgency or urge incontinence) for ≥ 3 months. There were 2225 patients enrolled; the Full Analysis Set (FAS) consisted of 2205 patients. The majority of the patients were female (82.2%) and Caucasian (79.9%), and the mean age was 59.7 years. Results are shown in Table 1.

Table 34. Efficacy Results After 12 Weeks of Treatment*

Assessment (n)	Mean Baseline	Mean Endpoint	Mean Change from Baseline to Endpoint	P-Value (95% CI)
PBC (2199)	4.4	2.9	-1.4	<0.001 (-1.49, -1.38)
VAS (mm) Urinary Urgency (1781)	68.7	29.1	-39.5	<0.001 (-41.0, -38.1)
Urge Incontinence (1504)	64.1	24.0	-40.1	<0.001 (-41.8, -38.4)
Frequency (1751)	70.6	28.8	-41.8	<0.001 (-43.3, -40.3)
Nocturia (1659)	65.2	28.3	-36.9	<0.001 (-38.4, -35.4)

*Full Analysis Set

PBC = Patient Perception of Bladder Condition Scale

VAS = Visual Analog Scale

Statistically significant improvements in patient PBC and VAS (for all four OAB symptoms) were seen at each study visit and maintained throughout the 12-week treatment phase. At baseline, frequency was the most bothersome symptom from patient reports and urge incontinence was the most bothersome symptom from physician's assessment. Patient perception of symptoms assessed using OAB-q demonstrated significant improvements in symptom severity, coping, concern, sleep, social interaction and health-related

quality of life (P < 0.001). After 12 weeks of therapy, 73.3% of patients experienced at least some improvement in PBC. The majority of patients reported improvement in symptoms measured by VAS including 88.2% for urgency,, 89.4% for urinary incontinence, 88.3% for frequency, and 87.5% for nocturia.

VESIcare was generally well-tolerated. Commonly reported adverse events included dry mouth (21.4%), constipation (13.3%), headache (3.4%), blurred vision (2.6%), nausea (1.8%), dyspepsia (1.5%) and dry eye (1.3%) the majority of which were considered to be of mild to moderate in severity. Overall, 9.7% of patients discontinued therapy due to an adverse event.

Ko et al. Study

Cost-Effectiveness of *VESIcare* Compared to Oxybutynin, Tolterodine, Darifenacin and Trospium

A pharmacoeconomic study was conducted to evaluate the cost-effectiveness of antimuscarinic therapies (oxybutynin immediate release 5 mg, oxybutynin extended release 10 mg, oxybutynin transdermal 3.9 mg, tolterodine immediate release 2 mg, tolterodine extended release 4 mg, darifenacin 15 mg, *VESIcare* 5 mg, and trospium 20 mg) for the treatment of OAB.[83] The three-month decision-analysis model was constructed from a payer's perspective to include clinical outcomes and cost for antimuscarinic therapy and treatment of OAB-associated comorbidites. Treatment success was defined as complete continence (no incontinence episodes or 7 consecutive dry days in a micturition diary) (Table 35). In each treatment arm, patients either continued the antimuscarinic therapy or discontinued due to adverse events. The patients who continue therapy experience either success (continence rate) or failure (1 - continence rate). Continence rates, discontinuation rates, comorbidity rates, and comorbidity treatment costs were obtained from separate published studies. Antimuscarinic therapy costs were based on 2005 average wholesale prices.

Table 35. Model Inputs for Continence and Discontinuation Rates [83]

Antimuscarinic therapy	**Continence rate (%)***	**Adverse-event related discontinuation rate (%)**
VESIcare 5 mg	50.3†	2.3
Oxybutynin transdermal 3.9 mg	39.0‡	10.7
Darifenacin 15 mg	24.0*	2.1
Oxybutynin extended release 10 mg	23.0§	5.1
Oxybutynin immediate release 5 mg	22.0§	21.0
Tolterodine extended release 4 mg	21.8‡§‖	4.0
Tolterodine immediate release 2 mg	21.0§	6.0
Trospium 20 mg	21.0¶	8.8
Continence and discontinuation rates for antimuscarinic therapies were based on multiple published studies.		
* Continence rates were taken from different trials; † Continence rate based on 3 consecutive days ‡ Continence rate based on last day of diary entry; § Continence rate based on 7-day diary; ‖ Rates are based on two different clinical trials; ¶ Continence period not provided.		

The results of this study suggested that *VESIcare* 5 mg was more effective and less costly than the other antimuscarinic agents (Table 36). However, because the primary model inputs (continence and discontinuation rates) were obtained from multiple studies, results should be interpreted with caution. Additional limitations included the following: the model did not consider other potential scenarios for OAB patients such as no treatment, treatment with non-pharmacologic therapies, dose titration with antimuscarinic therapy, switch in therapy, or medication compliance rates; model cost outputs are driven by the occurrence of comorbidities that have been associated with OAB, rather than directly caused by OAB; rates of comorbidities were all obtained from a single source, the NOBLE survey, which introduces the possibility of selection bias; and the model did not consider other commonly associated comorbidities with OAB such as vulval vaginitis.

Table 36. Cost, Effectiveness, and Cost-Effectiveness Ratios of each Antimuscarinic Therapy[83]

Antimuscarinic Therapy	Cost /3 months ($)	Effectiveness	Cost-Effectiveness Ratio ($)
VESIcare 5 mg	3373	0.491	6863
Oxybutynin transdermal 3.9 mg	3603	0.348	10,346
Darifenacin 15 mg	3633	0.235	15,462
Oxybutynin extended release 10 mg	3646	0.218	16,704
Oxybutynin immediate release 5 mg	3769	0.174	21,685
Tolterodine extended release 4 mg	3659	0.209	17,486
Tolterodine immediate release 2 mg	3750	0.197	18,999
Trospium 20 mg	3722	0.192	19,434

2.4 Evidence Table for Outcome Studies and Economic Evaluation

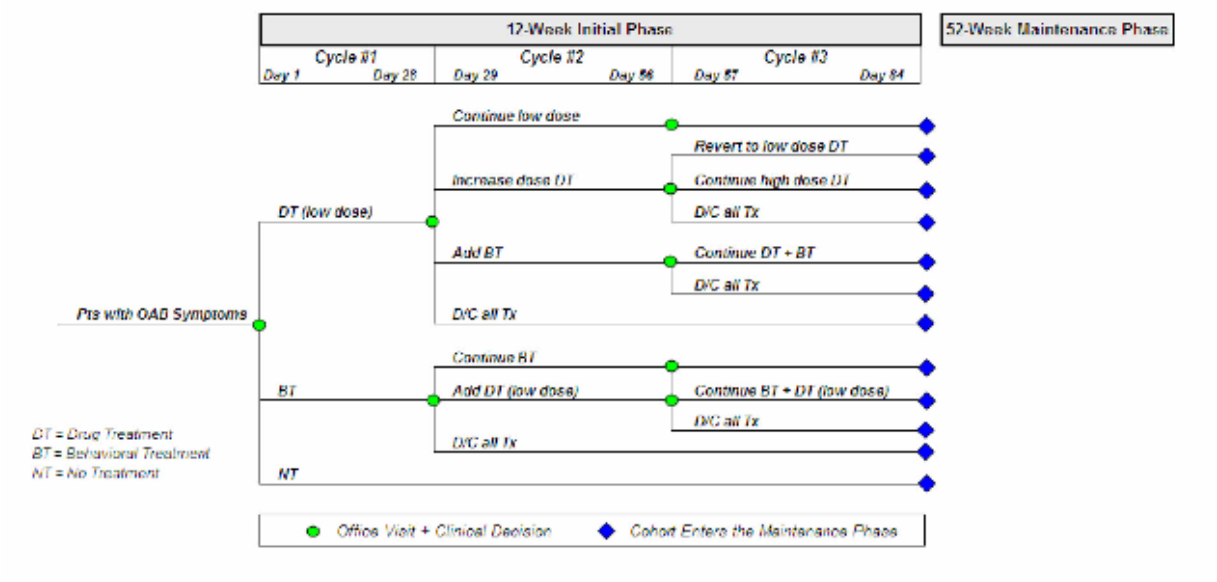
Table 37. - See Appendix

3. PHARMACOECONOMIC MODEL

Model of cost-effectiveness of Drug therapy, behavioral therapy and no therapy

The functional outcomes and cost-effectiveness of managing OAB with three treatment pathways was evaluated in a general practice setting.[84] An intent-to-treat decision analysis model, developed in a Microsoft Excel platform, compared the 15-month subjective symptom improvement and cost-effectiveness (payer's perspective) of no therapy, initial drug therapy, or initial behavioral therapy (8 sessions over 12 weeks). Baseline estimates of behavioral therapy costs, drug therapy costs, resource use (office visits, procedure/tests, treatment), effectiveness, persistence, and incidence/costs of OAB-related comorbid conditions (urinary tract infections, bone fractures, skin infections, vulvovaginitis and depression) were drawn from published literature. The model assumed therapeutic switching and a decline in persistence over the initial 12 weeks of treatment. The primary analysis assumed the use of a hypothetical once-daily oral drug therapy with characteristics of those reported for available antimuscarinic agents. Secondary analyses evaluated results when specific antimuscarinics were assumed as initial drug therapy and continence was used as the efficacy endpoint. Figure 8 shows a schematic of the intent-to-treat model including a 12-week initial phase and a 1 year maintenance phase.

Figure 8. Model Simulating Primary Care Management of Overactive Bladder (OAB)



Functional outcomes were lowest (0% subjective improvement) in untreated patients. In the behavioral therapy arm, the model estimated that 18% of patients would remain treated with initial behavioral therapy at the end of 15 months, 27% will have persisted with combined therapy (initial course of behavioral therapy + subsequent drug therapy), and 55% will have discontinued treatment. The model estimated that 45.1% of patients beginning with behavioral therapy will have realized subjective improvement. In the drug therapy arm, at the end of 15 months, the model estimated that 86% of patients remained on drug therapy alone (77% on low dose), 3% will have realized symptom improvement with combination therapy (initial course of behavioral therapy + subsequent drug therapy), and 11% will have discontinued treatment. In all, 89.2% of patients beginning with drug therapy will have subjective symptom improvement.

The average 12-week costs (exclusive of comorbid conditions) were $411 for untreated patients, $852 for patients initially treated with behavioral therapy, and $685 for patients initially treated with drug therapy. Average 15-month costs were $1,221 for OAB untreated patients. The 15-month average cost per patient with continued and successful treatment was $3,900 for patients treated with initial behavioral therapy and $2,323 for patients treated with initial drug therapy. Relative to no therapy, the incremental cost-effectiveness ratio of initial behavioral therapy and initial drug therapy were $1,193 and $955, respectively. Results were robust over a wide range of sensitivity analyses which varied treatment costs, efficacy, and persistence.

Secondary analyses evaluated the use of solifenacin (flexible dosing with 5 mg and 10 mg) or tolterodine ER (4 mg once daily, with no dosing flexibility) as initial drug therapy, and continence as the efficacy endpoint. When solifenacin was modeled as initial drug therapy, it was estimated that 57.2% of patients would achieve continence and remain persistent with drug therapy alone at the end of 15 months, 3.3% would be continent and persistent with combination therapy, and 39.5% would discontinue treatment. The 15-month average cost-effectiveness with initial solifenacin was $2,184 versus $3,816 with initial behavioral therapy. When tolterodine ER is modeled as initial drug therapy, the model estimated that, at the end of 15 months, 44.4% of patients would achieve continence and remain persistent with drug therapy alone, 3.2% would be continent and persistent with combination therapy and 52.4% would discontinue treatment. The 15-month average cost-effectiveness with initial behavioral therapy versus tolterodine ER was $4,044 and $3,450, respectively. This secondary analysis demonstrates that choice of initial drug therapy is also critical.

Limitations of the study include: inclusion of only incident OAB cases in an outpatient setting; use of simplified switching patterns; omission of the effects of copays or rebates; subjective versus objective evaluation of efficacy; inability to accommodate variation in baseline severity of symptoms, responses to therapy, decline in therapeutic efficacy or persistence over time, or the possibility of spontaneous resolution of symptoms without treatment; lack of workplace productivity and quality of life endpoints.

4. PRODUCT VALUE AND OVERALL COST

Background

- Overactive bladder (OAB) is a highly prevalent and costly condition that significantly affects a patients' quality of life. Patient fear of leakage (driven by embarrassment and social stigma) can result in significant lifestyle modifications.
- Based on published survey results of The National Overactive Bladder Evaluation (NOBLE) study, the overall prevalence of OAB is 16.9% in women and 16.2% in men, with an increase in OAB symptoms with advancing age.
- Patients who have OAB generally complain of urinary urgency with or without incontinence, urinary frequency (≥ 8 voiding episodes per 24 hours) and nocturia (awakening ≥ 1 time per night to void).
- Antimuscarinic agents are the mainstay of OAB treatment.
- VESIcare® (solifenacin succinate) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.
- The recommended dose of *VESIcare* is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.
- Other antimuscarinic agents indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency and urinary frequency include Ditropan XL® (oxybutynin chloride), Oxytrol® (oxybutynin transdermal system), Detrol, Detrol®LA (tolterodine tartrate), Sanctura®, Sanctura XR® (trospium chloride) and Enablex® (darifenacin).
- *VESIcare*, Ditropan XL, Detrol LA, Sanctura XR and Enablex may be administered once daily. Sanctura is administered twice daily and Oxytrol is applied every 3 to 4 days.
- Typically, common adverse events reported with antimuscarinic agents include dry mouth, constipation, blurred vision and dyspepsia.

Efficacy

- *VESIcare* was evaluated in four 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with a predominance of urge).
- Two of the four trials evaluated *VESIcare* 5 mg and 10 mg and the other two trials evaluated *VESIcare* 10 mg.
- Results of the individual studies showed that across all trials both doses of *VESIcare* statistically significantly reduced episodes of urgency, incontinence, and frequency per 24 hours, and statistically significantly increased volume voided per micturition compared with placebo.
- More than half of the patients experiencing incontinence at baseline reported no incontinence episodes at endpoint (51% of patients receiving *VESIcare* 5 mg and 52% of patients receiving *VESIcare* 10 mg compared to 34% for placebo; $P < 0.001$ for both doses).
- *VESIcare* was also evaluated in a 12-week, prospective, multicenter, randomized, placebo-controlled, double-blind trial in patients with urgency associated with OAB (VENUS).
- Patients treated with *VESIcare* reported a significantly greater reduction in urgency episodes/24 hours from baseline to end of study compared to patients treated with placebo. *VESIcare* significantly increased the amount of Warning Time from baseline to end of study compared to placebo ($P = 0.008$).
- Patients treated with *VESIcare* reported significantly greater changes from baseline to end of study in micturition frequency/24 h ($P = 0.0014$) and incontinence episodes/24 h compared with placebo ($P < 0.0001$). There was no statistical difference between *VESIcare* and placebo in the reduction of nocturia episodes or nocturnal voids.
- The effect of *VESIcare* on patient-reported outcomes was assessed in a prospective, open-label multicenter study in patients with symptoms of OAB (VOLT). After 12 weeks of therapy, 73.3% of patients experienced at least some improvement in patient perception of bladder condition. The majority of patients reported improvement in symptoms measured by visual analog scale including 88.2% for urgency, 89.4% for urinary incontinence, 88.3% for frequency, and 87.5% for nocturia.

Long-Term Efficacy

- A long-term, 40-week open-label extension study was conducted to evaluate the safety and tolerability along with the efficacy of *VESIcare*. A total of 81% of enrolled patients completed the additional 40-week treatment period.
- The most common adverse events reported in patients treated with *VESIcare* were dry mouth, constipation, blurred vision and dyspepsia, and the incidence appeared to be dose related.
- The favorable safety and tolerability profile of *VESIcare* observed during the initial 12 weeks of treatment appeared to be maintained in the open-label extension study over a 40-week period.

Efficacy in Elderly Patients

- In placebo-controlled clinical studies, similar safety and effectiveness were observed between older (623 patients ≥ 65 years and 189 patients ≥ 75 years) and younger patients (1188 patients < 65 years) treated with *VESIcare*.
- A post-hoc analysis of pooled data from four pivotal clinical trials revealed that treatment with *VESIcare* 5 mg and 10 mg once daily was associated with statistically significant reductions compared to placebo in micturitions, incontinence episodes, volume voided, and urgency episodes in patients ≥ 65 years of age.
- The most common adverse events reported in elderly patients treated with *VESIcare* in clinical trials and were dry mouth, constipation, and urinary tract infection.

Comparative Efficacy

- *VESIcare* has not been studied in comparative clinical trials with oxybutynin, trospium or darifenacin, however, a head-to-head study comparing *VESIcare* with tolterodine extended release has been conducted.
- A clinical trial with Solifenacin in a flexible-dose regimen compared with Tolterodine extended release as an Active comparator, was conducted in the Randomized (STAR) trial. This was a 12-week, double blind, double-dummy, comparative study to assess the efficacy and safety of *VESIcare* 5 mg or 10 mg once daily compared with tolterodine 4 mg extended release once daily (European formulation) in patients with OAB.
- The primary efficacy endpoint analysis of mean change from baseline to endpoint in the number of micturitions/24 hours established noninferiority of *VESIcare* compared with tolterodine extended release.
- The secondary endpoint analysis of percentage of incontinent patients at baseline reporting no incontinence episodes at endpoint established superiority of *VESIcare* (59%) compared with tolterodine extended release 4 mg (49%), as measured by 3-day patient diaries. This difference was statistically significant ($P = 0.006$).
- Other secondary endpoint analyses, mean change from baseline to endpoint in: incontinence episodes/24 hours; urge incontinence episodes/24 hours; pads used/24 hours; urgency episodes/24 hours; volume voided per micturition; and patient Perception of Bladder Condition (PBC) also demonstrated statistically significant superiority of *VESIcare* when compared with tolterodine 4 mg extended release.
- There was no significant difference between *VESIcare* and tolterodine extended release 4 mg in the reduction of nocturia episodes.
- The most common treatment-related adverse events reported in ≥ 2% of patients treated with *VESIcare* and tolterodine extended release were dry mouth, constipation and headache.
- Overall, 3.5% of patients treated with *VESIcare* and 3.0% of patients in the tolterodine extended release arm discontinued therapy due to all adverse events.

Safety

- In placebo-controlled clinical studies, common adverse events reported in patients treated with *VESIcare* were dry mouth, constipation, blurred vision and dyspepsia, and the incidence appeared to be dose related.

- Dry mouth was reported in 4.2%, 10.9% and 27.6% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Constipation was reported in 2.9%, 5.4%, and 13.4% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Blurred vision was reported in 1.8%, 3.8%, and 4.8% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively. Dyspepsia was reported in 1.0%, 1.4%, and 3.9% of patients receiving placebo, *VESIcare* 5 mg, and *VESIcare* 10 mg, respectively.
- Overall, in placebo-controlled clinical studies, 5.4% of patients receiving placebo, 3.6% of patients receiving *VESIcare* 5 mg and 6.9% of patients receiving *VESIcare* 10 mg discontinued therapy due to all adverse events.
- In placebo-controlled clinical studies, analysis of routine clinical laboratory parameters indicated no evidence of influence of *VESIcare* on hematology analytes, clinical chemistry analytes, or urinalysis parameters.
- In placebo-controlled clinical studies, analysis of vital signs data showed no evidence of influence of *VESIcare* on systolic blood pressure, diastolic blood pressure, or pulse rate.

Contraindications and Precautions

- *VESIcare* is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.
- *VESIcare*, like other anticholinergic drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.
- *VESIcare*, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.
- *VESIcare* should be used with caution in patients being treated for narrow-angle glaucoma.
- *VESIcare* should be used with caution in patients with reduced renal function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min).
- *VESIcare* should be used with caution in patients with reduced hepatic function. Doses of *VESIcare* greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). *VESIcare* is not recommended for patients with severe hepatic impairment (Child-Pugh C).
- Do not exceed a 5 mg daily dose of *VESIcare* when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.
- In a study of the effect of *VESIcare* on the QT interval in 76 healthy women, the QT prolonging effect appeared less with *VESIcare* 10 mg than with 30 mg (3 times the maximum recommended dose), and the effect of *VESIcare* 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe *VESIcare* for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

Pharmacoeconomics

- The estimated costs of OAB were more than $12 billion in the year 2000.
- OAB is associated with an increased risk and prevalence of comorbidities, the most common being urinary tract infections (UTIs), falls and fractures, depression and skin infections/irritations that add significantly to the overall cost of these patients to managed care.
- In addition to the contribution of comorbidities to the cost of illness of a condition, patient persistence with therapy also influences this burden.
- In an intent-to-treat decision analysis model evaluating average 15-month costs, initial treatment with drug therapy was more cost-effective than no therapy or initial behavioral therapy.
- Patient-reported outcomes were collected as secondary endpoints in an open-label, multicenter study of patients who wished to switch from tolterodine ER to *VESIcare* for the treatment of OAB symptoms. Based on the Medical Care Use Index (MCUI) data, patients experienced a significant reduction in number of physician visits, frequency of urinary tract infections, and quantity of pads/diapers used weekly from the pre-washout period to Week 12 of *VESIcare* therapy. The use of *VESIcare* resulted in improvements in medical resource utilization over pre-washout (tolterodine ER). *VESIcare* resulted in an estimated annual cost savings of $362 to $615 per patient year.

- A three-month decision-analysis model was constructed to evaluate the cost-effectiveness of antimuscarinic therapies (oxybutynin immediate release 5 mg, oxybutynin extended release 10 mg, oxybutynin transdermal 3.9 mg, tolterodine immediate release 2 mg, tolterodine extended release 4 mg, darifenacin 15 mg, *VESIcare* 5 mg, and trospium 20 mg) for the treatment of overactive bladder (OAB). Continence rates, discontinuation rates, comorbidity rates, and comorbidity treatment costs were obtained from published literature. The results of this study suggested that *VESIcare* 5 mg was more effective and less costly than the other antimuscarinic agents.
- The average wholesale price (AWP) for *VESIcare* 5 mg or 10 mg is $4.39 per tablet. The wholesale acquisition cost (WAC) for *VESIcare* 5 mg or 10 mg is $3.51 per tablet.

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Appendix

Table 5. Pharmacokinetics of Solifenacin, Oxybutynin, Tolterodine, Trospium and Darifenacin*

	VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Absorption	Tmax: 3 to 8 h Absolute bioavailability: 90% Not affected by food	Tmax: IR ≈ 1 hour; XL ≈12-13 h; TD ≈ 24-48 h Absolute bioavailability IR/XL: 6% Oral tablets not affected by food Oxybutynin solution co-administered with food results in a slight delay in absorption and an increase in bioavailability by 25%	Tmax: IR ≈ 2 h ; LA ≈ 4 h Absolute bioavailability: 77% Food increases bioavailability of IR by 53%- No dosage adjustment necessary	Tmax IR: 5-6 h post-dose; XR = 5 h post-dose Absolute bioavailability < 10% Administration of IR with a high fat meal decreases AUC and Cmax by 70-80% compared to administration while fasting. Administration of XR immediately after a high (50%) fat meal decreases AUC by 35% and Cmax by 60%	Tmax: ~ 7 h after multiple dosing 7.5 mg and 15 mg Mean oral bioavailability in EMs ~15% (7.5 mg) and ~19% (15 mg) Not affected by food
Distribution	98% protein bound Vd: 600 L	Vd: 193 L	Highly bound to plasma proteins Vd: 113 L	Protein binding: IR 50-85%; XR 48-78% Vd: IR = 395 L; XR = >600 L	98% bound to plasma proteins Vd: 163 L
Metabolism	Site: liver Primary pathway: CYP3A4 Active metabolites: 4R-hydroxy solifenacin	Site: liver Primary pathway: CYP3A4 Active metabolites: desethyloxybutynin	Site: liver Primary pathway: CYP2D6 Active metabolites: 5-hydroxymethyl tolterodine	Site: liver Primary pathway: ester hydrolysis with subsequent conjugation of benzylic acid to form azoniaspironortropanol with glucuronic acid	Site: liver Mediated by CYP2D6 and CYP3A4 Metabolic routes are by monohydroxylation and N-dealkylation Metabolites are unlikely to contribute significantly to clinical effect

* Based on manufacturer's full prescribing information

Tmax = time to maximum concentration; Vd = volume of distribution; CYP = cytochrome P450 isoenzyme system; $T_{1/2}$ = half life; AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; IR= Immediate Release; XL = Long-Acting Oxybutynin; XR = Extended-Release Trospium; LA= Long-Acting Tolterodine; TD = Transdermal; EMs = extensive metabolizers; PMs = poor metabolizers

	VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Excretion	Urine: 69.2% of administered dose (15% as parent compound) Feces: 22.5% of administered dose $t_{1/2}$: ≈ 50 h (45 to 68 h)	Less than 0.1% of administered dose recovered in urine $t_{1/2}$: IR ≈2-3 hours; XL ≈ 13 hours; TD ≈ apparent $t_{1/2}$ of 7-8 h	Urine: 77% of administered dose (< 1% as parent compound) Feces: 17% of administered dose $t_{1/2}$: IR ≈ 2.2 (9.6 h in poor metabolizers); LA ≈ 6.9 hours in extensive metabolizers Clearance: 11 L/h (415 L/h in poor metabolizers)	Urine: 5.8% of administered dose recovered in urine (60% as unchanged trospium) Feces: 85.2% of administered dose recovered in the feces $t_{1/2}$: IR ≈ 18.3 hours; XR ≈ 35-36 Mean renal clearance: 29.07 L/h (indicates active tubular secretion is a major route of elimination)	Urine: 60% recovered in urine Feces: 40% recovered in feces 3% of excreted dose was unchanged $t_{1/2}$: ≈ 13-19 h in EMs and PMs
Geriatric patients	In placebo controlled clinical studies, similar safety and effectiveness were observed between older and younger patients treated with *VESIcare*. Multiple dose studies of VESIcare in elderly volunteers (65 to 80 years) showed that Cmax, AUC, and $t_{1/2}$ values were 20-25% higher as compared to the younger 76 volunteers (18 to 55 years).	IR: Half-life increases to 5 hours in subjects over 65 years of age	Mean serum concentration of tolterodine and active metabolite were 20% to 50% higher, respectively, in healthy volunteers ages 71 to 81 than in young healthy volunteers No overall differences in safety between younger and older patients	IR: Age did not appear to significantly affect the pharmacokinetics of trospium, however, increased anticholinergic side effects unrelated to drug exposure were observed in patients ≥ 75 years of age XR: Compared to younger patients, patients ≥ 65 years of age reported a higher incidence of dry mouth, constipation, abdominal pain, dyspepsia, urinary tract infection, and urinary retention	Clearance tends to decrease with age Volunteers aged 45-65 years had a 12%-19% higher darifenacin exposure at steady state compared to those aged 18-44 years

***** Based on manufacturer's full prescribing information

Tmax = time to maximum concentration; Vd = volume of distribution; CYP = cytochrome P450 isoenzyme system; $T_{1/2}$ = half life; AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; IR= Immediate Release; XL = Long-Acting Oxybutynin; XR = Extended-Release Trospium; LA= Long-Acting Tolterodine; TD = Transdermal; EMs = extensive metabolizers; PMs = poor metabolizers

	VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Renal impairment	There is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with severe renal impairment	There is no experience with the use of Ditropan XL or Oxytrol in patients with renal insufficiency	In a study conducted in patients with creatinine clearance between 10 and 30 mL/min, tolterodine immediate release and the 5-hydroxymethyl metabolite levels were approximately 2-3 fold higher in patients with renal impairment than in healthy volunteers	A 4.5-fold and 2-fold increase in mean $AUC_{0-\infty}$ and Cmax, respectively, and the appearance of an additional elimination phase with a long half-life (~33 hr) was detected in patients with severe renal insufficiency (CLcr < 30 mL/min) compared with healthy, nearly age-matched subjects. The pharmacokinetics of trospium have not been studied in people with moderate or mild renal impairment (CLcr ranging from 30-80 mL/min)	A study with darifenacin 15 mg to steady state in subjects with varying degrees of renal impairment (CLcr 10 mL/min to 136 mL/min) demonstrated no clear relationship between renal function and clearance

* Based on manufacturer's full prescribing information

Tmax = time to maximum concentration; Vd = volume of distribution; CYP = cytochrome P450 isoenzyme system; $T_{1/2}$ = half life; AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; IR= Immediate Release; XL = Long-Acting Oxybutynin; XR = Extended-Release Trospium; LA= Long-Acting Tolterodine; TD = Transdermal; EMs = extensive metabolizers; PMs = poor metabolizers

	VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Hepatic impairment	There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment	There is no experience with the use of Ditropan XL or Oxytrol in patients with hepatic insufficiency	In a study of tolterodine immediate release conducted in cirrhotic patients, the elimination half-life of tolterodine immediate release was longer in cirrhotic patients (mean: 7.8 h) than in healthy, young and elderly volunteers (mean: 2-4 h). The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients (1 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg)	There is no information regarding the effect of severe hepatic impairment on exposure to trospium. Cmax increased 12% and 63% in subjects with mild and moderate hepatic impairment, respectively, compared to healthy subjects. Mean area under the plasma concentration-time curve (AUC) was similar	Pharmacokinetics were investigated in patients with mild or moderate hepatic impairment (Child-Pugh A and B) Mild hepatic impairment had no effect on pharmacokinetics Protein binding of darifenacin was affected by moderate impairment After adjusting for protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function No studies have been performed in patients with severe hepatic impairment (Child-Pugh C)

***** Based on manufacturer's full prescribing information

Tmax = time to maximum concentration; Vd = volume of distribution; CYP = cytochrome P450 isoenzyme system; $T_{1/2}$ = half life; AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; IR= Immediate Release; XL = Long-Acting Oxybutynin; XR = Extended-Release Trospium; LA= Long-Acting Tolterodine; TD = Transdermal; EMs = extensive metabolizers; PMs = poor metabolizers

Table 6. Potential Drug Interactions for *VESIcare*, Oxybutynin, Tolterodine, Trospium and Darifenacin*

VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Cytochrome P450: At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. CYP3A4 Inhibitors: In vitro drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics.	Anticholinergics: Concomitant use with oxybutynin may increase the frequency and/or severity of anticholinergic effects, and may alter the absorption of some drugs due to anticholinergic effects on gastrointestinal motility which may be a concern for drugs with a narrow therapeutic index. Ketoconazole: Co-administration of oxybutynin with ketoconazole resulted in a mean 2-4 fold increase in oxybutynin plasma concentrations. Other CYP3A4 inhibitors, such as azole antifungals and macrolide antibiotics may alter the pharmacokinetics of oxybutynin.	Cytochrome P450: In vivo drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2C9, 2C19, 2D6, or 3A4. CYP2D6 Inhibitors: The primary metabolic pathway of tolterodine is mediated by CYP2D6. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in Cmax and a 20% decrease in AUC of the 5-hydroxymethyl metabolite.	Based on in vitro data, no clinically relevant metabolic drug-drug interactions are anticipated with trospium. However, some drugs which are actively secreted by the kidney may interact with trospium by competing for renal tubular secretion. Antimuscarinic Agents: Combined use with trospium may increase the frequency and/or severity of anticholinergic effects. Trospium may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on GI motility. Digoxin: Concomitant use of trospium 20 mg BID and digoxin did not affect the pharmacokinetics of either drug.	Cytochrome P450: Darifenacin metabolism is primarily mediated by CYP2D6 and CYP3A4. Therefore, inducers or inhibitors of these enzymes could potentially alter darifenacin pharmacokinetics. Based on in vitro studies, darifenacin is not expected to inhibit CYP1A2 or CYP2C9 at clinically relevant concentrations. CYP2D6 Inhibitors: No dosage adjustment of darifenacin is recommended when given concomitantly with CYP2D6 inhibitors. CYP3A4 Inhibitors: When given concomitantly with CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, nefazodone) the maximum daily dose of darifenacin should not exceed 7.5 mg. .
* Based on manufacturer's full Prescribing Information				

VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Ketoconazole Interaction Study: Following the administration of 10 mg of *VESIcare* in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean Cmax and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5 mg daily dose of *VESIcare* when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. Oral Contraceptives: In the presence of solifenacin there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levonorgestrel).		Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and the 5-hydroxymethyl metabolite are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are coadministered. CYP3A4 Inhibitors: In the presence of ketoconazole 200 mg, the mean Cmax and AUC of tolterodine immediate release was increased by 2 and 2.5 fold, respectively in subjects known to metabolize tolterodine via CYP3A4 because these patients were known to be poor metabolizers of the CYP2D6 enzyme.	Antacid: In a drug interaction study (n=11), the systemic exposure of trospium extended release on average was comparable with and without antacid,5 individuals demonstrated either an increase or decrease in trospium exposure, in presence of an antacid containing aluminum hydroxide and magnesium carbonate.	Dosage adjustments are not necessary when given concomitantly with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil) CYP2D6 Substrates: Use caution when darifenacin is coadministered with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window such as flecainide, thioridazine and tricyclic antidepressants. CYP3A4 Substrates: Following a single oral dose of 7.5 mg, a 17% increase in the midazolam concentration (a CYP3A4 substrate) was observed following coadministration with darifenacin 30 mg daily.
* Based on manufacturer's full Prescribing Information				

VESIcare	**Oxybutynin**	**Tolterodine**	**Trospium**	**Darifenacin**
Warfarin: Solifenacin has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin. Digoxin: Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.		Based on these findings, other potent CYP3A4 inhibitors such as other azole antifungals, macrolide antibiotics, cyclosporine, or vinblastine may also lead to increases in tolterodine plasma concentrations. Warfarin: In healthy volunteers, coadministration of tolterodine immediate release 4 mg for 7 days and a single dose of warfarin 25 mg on day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin Oral Contraceptives: Tolterodine immediate release 4 mg had no effect on the pharmacokinetics of the oral contraceptive ethinyl estradiol/levonorgestrel over a 2 month period in healthy volunteers. Diuretics: Co-administration of tolterodine immediate release (≤ 8 mg) for up to 12 weeks with diuretics such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide or furosemide did not cause any adverse electrocardiographic effects.		The pharmacokinetics of the combination oral contraceptive ethinyl estradiol/levonorgestrel was not affected by darifenacin (10 mg 3 times daily). Warfarin: Darifenacin had no significant effect on prothrombin time when a single dose of warfarin 30 mg was coadministered with darifenacin 30 mg. Standard therapeutic prothrombin time monitoring for warfarin should be continued. Digoxin: Routine digoxin drug monitoring should continue. At steady state, a 16% increase in digoxin concentrations was observed following coadministration with darifenacin (30 mg daily).
* Based on manufacturer's full Prescribing Information				

Table 7. Dosage and Availability of *VESIcare*, Oxybutynin, Tolterodine, Trospium and Darifenacin*

Product	Dosage Strength Availability	Dosage
VESIcare	5 mg and 10 mg tablets	The recommended dose of *VESIcare* is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily *VESIcare* should be taken with liquids and swallowed whole. *VESIcare* can be administered with or without food For patients with severe renal impairment (CLcr < 30 mL/min), a daily dose of *VESIcare* greater than 5 mg is not recommended For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of *VESIcare* greater than 5 mg is not recommended. Use of *VESIcare* in patients with severe hepatic impairment (Child-Pugh C) is not recommended When administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors, a daily dose of *VESIcare* greater than 5 mg is not recommended
Oxybutynin	5 mg tablets 5 mg/5 mL syrup	Recommended starting dose is 5 mg 2 to 3 times a day. The maximum recommended dose if 5 mg 4 times a day. A lower starting dose of 2.5 mg is recommended for the frail elderly In pediatric patients (> 5 years) the recommended starting dose is 5 mg twice daily. The maximum recommended dose is 5 mg 3 times a day
	5 mg, 10 mg and 15 mg extended-release tablets	Recommended starting dose is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustments may proceed at approximately weekly intervals Must be taken with liquids and swallowed whole. May be administered with or without food. In pediatric patients (≥6 years) the recommended starting dose is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day)
	3.9 mg/day transdermal system	3.9 mg/day system applied twice weekly (every 3 to 4 days) Should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new system to avoid re-application to the same site within 7 days.
* Based on manufacturer's full Prescribing Information		

Product	Dosage Strength Availability	Dosage
Tolterodine	1 mg and 2 mg tablets	Recommended starting dose is 2 mg twice daily. May be reduced to 1 mg twice daily based on individual response and tolerability For patients with significantly reduced renal or hepatic function or who are taking potent inhibitors of CYP3A4, the recommended dose is 1 mg twice daily
	2 mg and 4 mg extended-release capsules	Recommended dose is 4 mg once daily. Should be taken with liquids and swallowed whole. Dose may be lowered to 2 mg daily based on individual response and tolerability In patients with reduced hepatic or renal function or those taking potent inhibitors of CYP3A4, the recommended dose is 2 mg once daily
Trospium	20 mg tablets	The recommended dose is 20 mg twice daily. Trospium should be dosed at least one hour before meals or given on an empty stomach For patients with severe renal impairment (CLcr < 30 mL/min), the recommended dose is 20 mg once daily at bedtime In geriatric patients ≥75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability
	60 mg extended-release capsules	The recommended dose is 60 mg once daily in the morning. Should be dosed with water on an empty stomach, at least one hour before a meal. Not recommended for use in patients with severe renal impairment (CLcr< 30 mL/min)
Darifenacin	7.5 mg and 15 mg extended-release tablets	The recommended starting dose is 7.5 mg once daily. Based upon individual response, the dose may be increased to 15 mg once daily, as early as 2 weeks after starting therapy The tablets should be taken with liquids and may be taken with or without food Tablets should swallowed whole and not chewed, divided or crushed The daily dose should not exceed 7.5 mg once daily in patients with moderate hepatic impairment (Child-Pugh B) or when given concomitantly with potent CYP3A4 inhibitors Not recommended for use in patients with severe hepatic impairment (Child-Pugh C)
* Based on manufacturer's full Prescribing Information		

Table 29. Key Clinical Studies for *VESIcare*

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Pivotal Study 015[59,60]	1. *VESIcare* 5 mg daily (n = 266) 2. *VESIcare* 10 mg daily (n = 264) 3. Tolterodine 2 mg BID (n = 250) 4. Placebo daily (n =253)	1033	• 2-week placebo run-in • 12 weeks of treatment	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms for ≥ 3 months • Mean micturition frequency ≥ 8/24 hours • ≥ 3 urinary incontinence episodes OR at least 3 urgency episodes over a 3-day period Demographics: • 75% female • 98% Caucasian • Mean age: 57 years	Randomized, double-blind, placebo-controlled, parallel, multicenter	Primary: Mean change from baseline to endpoint • Number of micturitions/24 hours – *VESIcare* 5 mg: -2.2 , $P < 0.001$ vs. placebo – *VESIcare* 10 mg: -2.6 , $P < 0.001$ vs. placebo – Tolterodine: -1.9, $P = 0.004$ vs. placebo – Placebo: -1.2 Secondary: Mean change from baseline to endpoint • Incontinence episodes/24 hours – *VESIcare* 5 mg: -1.4, $P < 0.01$ vs. placebo – *VESIcare* 10 mg: -1.5, $P < 0.01$ vs. placebo – Tolterodine: -1.1, $P = 0.017$ vs. placebo – Placebo: -0.8 • Urgency episodes/24 hours – *VESIcare* 5 mg: -2.9, $P < 0.001$ vs. placebo – *VESIcare* 10 mg: -3.1, $P < 0.001$ vs. placebo – Tolterodine: -2.1, $P = 0.043$ vs. placebo – Placebo: -1.4 • Volume voided/micturition – *VESIcare* 5 mg: +32.9 mL, $P < 0.001$ vs. placebo – *VESIcare* 10 mg: +39.2 mL, $P < 0.001$ vs. placebo – Tolterodine: +24.4, $P < 0.001$ vs. placebo – Placebo: +7.4

Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Pivotal Study 015[59,60]	See above		See above	See above	See above	• Most common treatment-related adverse effects: – Dry Mouth: o *VESIcare* 5 mg: 14% o *VESIcare* 10 mg: 21.3% o Tolterodine: 18.6% o Placebo: 4.9% – Constipation: o *VESIcare* 5 mg: 7.2% o *VESIcare*10 mg: 7.8% o Tolterodine: 2.7% o Placebo: 1.9% – Blurred Vision: o *VESIcare* 5 mg: 3.6% o *VESIcare*10 mg: 5.6% o Tolterodine: 1.5% o Placebo: 2.6%
Pivotal Study 018[61,62]	1. *VESIcare* 5 mg daily (n = 286) 2. *VESIcare* 10 mg daily (n = 290) 3. Placebo daily (n =281)	857	• 2-week placebo run-in • 12 weeks of treat-ment	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms for ≥ 3 months • Mean micturition frequency ≥ 8/24 hours • ≥ 3 urinary incontinence episodes OR ≥ 3 urgency episodes over a 3-day period Demographics: • 82% female • 97% Caucasian • Mean age: 56 years	Randomized, double-blind, placebo-controlled, parallel, multicenter	Primary: Mean change from baseline to endpoint • Number of micturitions/24 hours – *VESIcare*5 mg: -2.4, $P < 0.001$ vs. placebo – *VESIcare* 10 mg: -2.9, $P < 0.001$ vs. placebo – Placebo: -1.7 Secondary: Mean change from baseline to endpoint • Incontinence episodes/24 hours – *VESIcare* 5 mg: -1.6, $P < 0.01$ vs. placebo – *VESIcare* 10 mg: -1.6, $P = 0.016$ vs. placebo – Placebo: -1.3
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Pivotal Study 018[61,62]	See above	See above	See above	See above	See above	• Urgency episodes/24 hours – *VESIcare* 5 mg: -3, $P = 0.005$ vs. placebo – *VESIcare* 10 mg: -3, $P = 0.0001$ vs. placebo – Placebo: -2.1 • Volume voided/micturition – *VESIcare* 5 mg: +31.8 mL, $P < 0.001$ vs. placebo – *VESIcare* 10 mg: +36.6 mL, $P < 0.001$ vs. placebo – Placebo: +11.3 Most common treatment-related adverse effects: • Dry Mouth: – *VESIcare* 5 mg: 7.4% – *VESIcare* 10 mg: 23.1% – Placebo: 2.3% • Constipation: – *VESIcare* 5 mg: 3.3% – *VESIcare* 10 mg: 8.8% – Placebo: 2% • Blurred Vision: – *VESIcare* 5 mg: 3.7% – *VESIcare* 10 mg: 5.5% – Placebo: 2.3%
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Pivotal Study 013[1,57]	1. *VESIcare* 10 mg daily (n = 306) 2. Placebo daily (n = 309)	615	• 2-week placebo run-in • 12 weeks of treatment	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms • Mean micturition frequency ≥ 8/24 hours • An average of ≥ 1 urinary incontinence episode/24 hours OR an average of ≥ 1 urgency episode/24 hours Demographics: • 82% female • 83% Caucasian • Mean age: 58 years	Randomized, double-blind, placebo-controlled, parallel, multicenter	Primary: Mean change from baseline to endpoint • Number of micturitions/24 hours – *VESIcare*: -3, $P < 0.001$ vs. placebo – Placebo: -1.5 Secondary: Mean change from baseline to endpoint • Incontinence episodes/24 hours – *VESIcare*: -2, $P < 0.001$ vs. placebo – Placebo: -1.1 • Urgency episodes/24 hours – *VESIcare*: -4.1, $P < 0.001$ vs. placebo – Placebo: -2.5 • Volume voided/micturition – *VESIcare*: +47.2 mL, $P < 0.001$ vs. placebo – Placebo: +2.7 mL Most common treatment-related adverse effects: • Dry Mouth: – *VESIcare*: 25.6% – Placebo: 3.6% • Constipation: – *VESIcare*: 16.2% – Placebo: 3.3% • Dyspepsia: – *VESIcare*: 3.8% – Placebo: 0.3% • Blurred Vision: – VESIcare: 3.2% – Placebo: 1.2% • Nausea: – *VESIcare*: 3.2% – Placebo: 1.8%
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Pivotal Study 014[58]	1. *VESIcare* 10 mg daily (n = 298) 2. Placebo daily (n = 295)	593	• 2-week placebo run-in • 12 weeks of treatment • 2-week post-treatment follow-up	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms • Mean micturition frequency ≥ 8/24 hours • An average of ≥ 1 urinary incontinence episode/24 hours OR an average of ≥ 1 urgency episode/24 hours Demographics: • 82% female • 90% Caucasian • Mean age: 60 years	Randomized, double-blind, placebo-controlled, parallel, multicenter	Primary: Mean change from baseline to endpoint • Number of micturitions/24 hours – *VESIcare*: -2.4, $P < 0.001$ vs. placebo – Placebo: -1.3 Secondary: Mean change from baseline to endpoint • Incontinence episodes/24 hours – *VESIcare*: -2, $P < 0.001$ vs. placebo – Placebo: -1.2 • Urgency episodes/24 hours – *VESIcare*: -3.3, $P < 0.001$ vs. placebo – Placebo: -1.8 • Volume voided/micturition – *VESIcare*: +46.4 mL, $P <0.001$ vs. placebo – Placebo: +13 mL Most common treatment-related adverse effects: • Dry Mouth: – *VESIcare*: 37.1% – Placebo: 5.7% • Constipation: – *VESIcare*: 17.6% – Placebo: 3.8% • Nausea: – *VESIcare*: 4.1% – Placebo: 1.3% • Dyspepsia: – VESIcare: 4.1% – Placebo: 0.9%

Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
Long-Term, Extension Study 019[22,66]	*VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg for a total of 40 weeks (dose changes were also optional at week 16 and week 28) (n = 1633)	1633	40 weeks (patients from 2 of the 12-week double-blind, randomized studies were eligible to enter this open label trial; duration of studies combined = 52 weeks)	Inclusion Criteria: • Previously enrolled in study 015 or 018 • Ages ≥ 18 years with OAB symptoms for ≥ 3 months • Mean micturition frequency ≥ 8/24 hours • ≥ 3 urinary incontinence episodes OR ≥ 3 urgency episodes over a 3-day period Demographics: • 78% female • 98% Caucasian • Mean age: 56 years	Non-randomized, open-label, multicenter, extension study	• 91% (1637/1802) of patients from the double-blind studies chose to enter the open-label trial • 42% of patients received *VESIcare* 5 mg for the entire 40-week extension trial • 51% of patients chose to increase their dose to 10 mg for the remainder of the study • 7% of patients increased their dose to 10 mg, but chose to decrease back to 5 mg before the end of the study Most common adverse effects • Dry Mouth – *VESIcare* 5 mg: 10.2% – *VESIcare* 10 mg: 17.4% • Constipation – *VESIcare* 5 mg: 4.9% – *VESIcare* 10 mg: 7.9% • Blurred Vision – *VESIcare* 5 mg: 4.1% – *VESIcare* 10 mg: 4.4% Mean change from original baseline to endpoint at 52 weeks (% change) • Number of micturitions/24 hours – *VESIcare*: -2.97 (23%) • Incontinence episodes/24 hours – *VESIcare*: -1.74 (66%) • Urgency episodes/24 hours – *VESIcare*: -3.48 (63%) • Volume voided/micturition – *VESIcare*: +39.8 mL (31%)
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
STAR[30]	1. *VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg daily x 8 weeks (dose increase at 4 weeks was optional) (n = 578) 2. Tolterodine ER 4 mg daily x 12 weeks (patients who requested a dose increase at 4 weeks received tolterodine ER 4 mg + placebo daily) (n = 599)	1177	• 2-week placebo run-in • 12 weeks of treat-ment	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms for ≥ 3 months • Mean micturition frequency ≥ 8/24 hours • ≥ 3 urinary incontinence episodes OR ≥ 3 urgency episodes over a 3-day period Demographics: • 87% female • 99.5% Caucasian • Mean age: 57 years	Randomized, double-blind, double-dummy, active-controlled, parallel, multicenter	Primary: (noninferiority) mean change from baseline to endpoint • Number of micturitions/24 hours – *VESIcare*: -2.45 – Tolterodine ER: --2.24, *P* = 0.004 vs. *VESIcare* Secondary: (superiority) mean change from baseline to endpoint • Incontinence episodes/24 hours – *VESIcare*: -1.6 – Tolterodine ER: -1.11, *P* = 0.006 vs. *VESIcare* • Urge incontinence episodes/24 hours – *VESIcare*: -1.42 – Tolterodine ER: -0.83, *P* = 0.001 vs. *VESIcare* • Pads used/24 hours – *VESIcare* : -1.72 – Tolterodine ER: -1.19, *P* = 0.002 vs. *VESIcare* • Urgency episodes/24 hours – *VESIcare*: -2.85 – Tolterodine ER: -2.42, *P* = 0.035 vs. *VESIcare* • Volume voided/micturition – *VESIcare*: +37.95 mL – Tolterodine ER: +31 mL, *P* = 0.010 vs. *VESIcare* • Patient Perception of Bladder Condition (PBC) – *VESIcare*: -1.51 – Tolterodine ER: -1.33, *P* = 0.006 vs. *VESIcare* • Percent of patients incontinent at baseline reporting no incontinence episodes at endpoint – *VESIcare*: 59% – Tolterodine ER: 49%, *P* = 0.006 vs. *VESIcare*

Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
STAR[30]	See above		See above	See above	See above	Common adverse effects (≥ 2% of patients): • Dry Mouth: – *VESIcare*: 30.0% – Tolterodine ER: 24.1% • Constipation: – *VESIcare*: 6.4% – Tolterodine ER: 2.5% • Headache: – *VESIcare*: 2.7% – Tolterodine ER: 3.6%
VENUS[71]	1. *VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg daily x 4 weeks, then *VESIcare* 5 mg or 10 mg x 4 weeks (dose increase at 4 weeks and increase/ decrease at 8 weeks was optional) (n = 357) 2. Placebo daily x 12 weeks (n =350)	707	• 2-week placebo run-in • 12 weeks of treat-ment	Inclusion Criteria: • ≥ 18 years with OAB symptoms for ≥ 3 months • Mean micturition frequency ≥ 8 episodes/24 hours and/or nocturia • An average of ≥ 1 urgency episode/24 hours (with or without urge incontinence) Demographics: • 84.2% female • 83.5% Caucasian • Mean age: 57 years	Randomized, double-blind, placebo-controlled, parallel, multicenter	Primary: Mean change from baseline to endpoint • Urgency episodes/24 hours – *VESIcare*: -3.91, $P < 0.0001$ vs. placebo – Placebo: -2.73 Secondary: Median change from baseline to endpoint • Warning Time – *VESIcare*: +31.5 seconds, $P = 0.008$ vs. placebo – Placebo: +12 seconds Secondary: Mean change from baseline to endpoint • Indevus Urgency Severity Scale – *VESIcare*: -0.9, $P < 0.0001$ vs. placebo – Placebo: -0.5
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Reference	Drug Regimens	N	Duration	Inclusion/Demographics	Study Design	Endpoints/Results
See above[71]		See above	See above	See above	See above	• Urgency Perception Scale – *VESIcare*: + 0.4, *P* = 0.0018 vs. placebo – Placebo: + 0.2 • Number of micturitions/24 hours – *VESIcare*: -2.67, *P* = 0.0014 vs. placebo – Placebo: -1.94: • Incontinence episodes/24 hours – *VESIcare*: -2.10, *P* < 0.001 vs. placebo – Placebo: -1.24: Treatment-related adverse effects: • Dry Mouth: – *VESIcare*: 25.3% – Placebo: 9% • Constipation: – *VESIcare*: 14.8% – Placebo: 9.3% • Blurred Vision: – *VESIcare*: 3.8% – Placebo: 1.1%
Abbreviations: ER = Extended Release, mL = Milliliters, OAB = Overactive Bladder, PO = by mouth, STAR = Solifenacin in a flexible-dose regimen with Tolterodine extended release as an Active comparator in a Randomized trial, VENUS = *VESIcare* Efficacy and safety in patieNts with Urgency Study						

Table 37. Outcome Studies and Economic Data for *VESIcare*

Reference	Drug Regimens	N	Duration	Inclusion/ Demographics	Study Design	Endpoints/Results
VERSUS[73]	*VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg daily x 4 weeks, then *VESIcare* 5 mg or 10 mg x 4 weeks (dose increase at 4 weeks and increase/decrease at 8 weeks was optional) (n = 441)	441	• 2-week washout • 12 weeks of treatment	Inclusion Criteria: • Ages ≥18 years with OAB symptoms for ≥ 3 months • ≥ 3 urgency episodes/24 hours while taking tolterodine ER • Tolterodine ER treatment for ≥ 4 weeks prior to study entry Demographics: • 88.2% female • 88.9% Caucasian • Mean age: 61.4 years	Non-randomized, prospective, open-label, multicenter	Primary: mean change from pre-washout to endpoint • Urgency episodes/24 hours – *VESIcare*: -3.41, *P* <0.0001 vs. pre-washout Secondary: mean change from pre-washout to endpoint • Number of micturitions/24 hours – *VESIcare*: -1.57, *P* <0.0001 vs. pre-washout • Incontinence episodes/24 hours – *VESIcare*: -1.86, *P* < 0.0001 vs. pre-washout • Nocturia episodes/24 hours – *VESIcare*: -0.72, *P* < 0.0001 vs. pre-washout • Nocturnal voids/24 hours – *VESIcare*: -0.79, *P* < 0.0001 vs. pre-washout • Patient Perception of Bladder Condition and each of the OAB-q subscales improved significantly from pre-washout (*P* < 0.0001). Common (≥4%) treatment-related adverse effects: • Dry Mouth: – *VESIcare*: 17.5% • Constipation: – *VESIcare*: 11.6% • Urinary Tract Infection: – *VESIcare*: 4.3%

Abbreviations: OAB = Overactive Bladder, OAB-q = Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire, UTI = Urinary Tract Infection, VERSUS = *VESIcare* Efficacy and Research Study US, VOLT = *VESIcare* Open-Label Trial

Reference	Drug Regimens	N	Duration	Inclusion/ Demographics	Study Design	Endpoints/Results
VERSUS Economic Analysis of Patient-Reported Outcomes (56)	*VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg daily x 4 weeks, then *VESIcare* 5 mg or 10 mg x 4 weeks (dose increase at 4 weeks and increase/decrease at 8 weeks was optional) (n = 441)	441	• 2-week washout • 12 weeks of treatment	Inclusion Criteria: • ≥ 18 years with OAB symptoms for ≥ 3 months • ≥ 3 urgency episodes/24 hours while taking tolterodine ER • Tolterodine ER treatment for ≥ 4 weeks prior to study entry Demographics: • 88.2% female • 88.9% Caucasian • Mean age: 61.4 years	Non-randomized, prospective, open-label, multicenter	Secondary endpoints Mean change from pre-washout to endpoint • Number of physician office visits: -0.99, $P < 0.0001$ vs. pre-washout • Number of UTIs: -0.12, $P < 0.0001$ vs. pre-washout • Number of pads/diapers used weekly: -2.96, $P = 0.0006$ • Number of skin rashes and number of falls were not statistically significant • Percent work missed due to bladder condition: -1.82, $P = 0.0024$ • Percent impairment while working due to bladder condition: -11.49, $P < 0.0001$ • Percent overall work impairment due to bladder condition: -12.10, $P < 0.0001$ • Percent activity impairment due to problem: -12.90, $P < 0.0001$ Calculated cost savings • Mean total annual costs (office visits, UTIs, pad/diaper costs) – Tolterodine Failure: $1117.15 – *VESIcare*: $503.24 • UTI and pad costs only – Tolterodine Failure: $806.50 – *VESIcare*: $440.10
Abbreviations: OAB = Overactive Bladder, OAB-q = Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire, UTI = Urinary Tract Infection, VERSUS = *VESIcare* Efficacy and Research Study US, VOLT = *VESIcare* Open-Label Trial						

Reference	Drug Regimens	N	Duration	Inclusion/ Demographics	Study Design	Endpoints/Results
VOLT[80,81,82]	*VESIcare* 5 mg daily x 4 weeks then *VESIcare* 5 mg or 10 mg daily x 4 weeks, then *VESIcare* 5 mg or 10 mg x 4 weeks (dose increase at 4 weeks and increase/decrease at 8 weeks was optional) (n = 2205)	2205	• 7-day washout for patients on other OAB medications then • 12 weeks of treatment with *VESIcare*	Inclusion Criteria: • Ages ≥ 18 years with OAB symptoms for ≥ 3 months Demographics: • 82.2% female • 79.9% Caucasian • Mean age: 59.7 years	Prospective, open-label, multicenter	Primary endpoint: mean change from baseline to endpoint • Patient Perception of Bladder Condition – *VESIcare* 1.4, $P < 0.0001$ vs. baseline • Visual Analog Scale – Urinary urgency: -39.5 mm, $P < 0.001$ vs. baseline – Urge Incontinence: -40.1 mm, $P < 0.001$ vs. baseline – Frequency: -41.8 mm, $P < 0.001$ vs. baseline – Nocturia: -36.9 mm, $P < 0.001$ vs. baseline Secondary endpoint • OAB-q – Significant improvement on all subscales, $P < 0.001$ vs. baseline (symptom severity, coping, concern, sleep, social interaction, and overall health-related quality of life)

Abbreviations: OAB = Overactive Bladder, OAB-q = Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire, UTI = Urinary Tract Infection, VERSUS = *VESIcare* Efficacy and Research Study US, VOLT = *VESIcare* Open-Label Trial

Reference	Drug Regimens	N	Duration	Inclusion/ Demographics	Study Design	Endpoints/Results
Ko[83]	• *VESIcare* 5 mg daily (n = 286) • Oxybutynin transdermal 3.9 mg twice weekly (n = 121) • Darifenacin 15 mg daily (n = 334) • Oxybutynin extended release 10 mg daily (n = 391) • Oxybutynin immediate release 5 mg TID (n = 112) • Tolterodine extended release 4 mg daily (n = 522) • Tolterodine immediate release 2 mg BID (n = 109) • Trospium 20 mg BID (n = 262)	2137	Costs predicted over a 3-month period	Model Inputs • Continence Rates (%) – *VESIcare* 50.3 – Oxybutynin transdermal 39.0 – Darifenacin 24.0 – Oxybutynin ER 23.0 – Oxybutynin IR 22.0 – Tolterodine ER 21.8 – Tolterodine IR 21.0 – Trospium 21.0 • Adverse-Event Related Discontinuation Rates (%) – *VESIcare* 2.3 – Oxybutynin transdermal 10.7 – Darifenacin 2.1 – Oxybutynin ER 5.1 – Oxybutynin IR 21.0 – Tolterodine ER 4.0 – Tolterodine IR 6.0 – Trospium 8.8	Decision analysis model from the payer's perspective to compare cost-effectiveness of antimuscarinics and treatment of OAB-associated comorbidities; data on continence and discontinuation rates from randomized, controlled trials	• Cost Per 3 months – *VESIcare* $3,373 – Oxybutynin transdermal $3,603 – Darifenacin $3,633 – Oxybutynin ER $3,646 – Oxybutynin IR $3,769 – Tolterodine ER $3,659 – Tolterodine IR $3,750 – Trospium $3,722 • Effectiveness – *VESIcare* 0.491 – Oxybutynin transdermal 0.348 – Darifenacin 0.235 – Oxybutynin ER 0.218 – Oxybutynin IR 0.174 – Tolterodine ER 0.209 – Tolterodine IR 0.197 – Trospium 0.192

Abbreviations: OAB = Overactive Bladder, OAB-q = Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire, UTI = Urinary Tract Infection, VERSUS = *VESIcare* Efficacy and Research Study US, VOLT = *VESIcare* Open-Label Trial